# STOP-HCV-1
# Stratified Treatment OPtimisation for HCV-1

**Version:** **7.0**
**Date:** **22-Feb-2018**

**ISRCTN #:** **ISRCTN#37915093**

**EUDRACT #:** **2015-005004-28**
**CTA #:** **19174/0370/001-0001**
**MREC #:** **15/EE/0435**

**Authorised by:**

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Date: 31-May-2018

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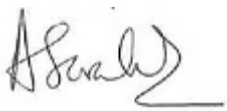

29-May-2018

# GENERAL INFORMATION

This document was constructed using the MRC CTU at UCL Protocol Template Version 4.0. The MRC CTU endorses the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT) initiative. It describes the STOP-HCV-1 trial, coordinated by the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL), and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering patients for the first time are advised to contact the Infections Theme, MRC CTU at UCL, London, UK, to confirm they have the most up-to-date version.

## COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the current version of the Declaration of Helsinki, the principles of Good Clinical Practice (GCP), Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act (DPA number: Z6364106), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). International sites will comply with the principles of GCP as laid down by the ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC (the European Directive 2001/20/EC) and applicable national regulations.

## SPONSOR

Imperial College London is the trial Sponsor and has delegated responsibility for pharmacovigilance, quality assurance and quality control, document management (including the Trial master file), database and archiving, regulatory and ethics approvals to the MRC CTU at UCL. Queries relating to sponsorship of this trial should be addressed to the Imperial Joint Research Compliance Office via the Chief Investigator.

## FUNDING

The trial is funded in principle by the Efficacy and Mechanism Evaluation (EME) Programme, a Medical Research Council (MRC) and National Institutes of Health Research (NIHR) partnership (14/02/17) (formal notification pending).

## AUTHORISATIONS AND APPROVALS

This trial was approved by the East of England - Cambridge South Research Ethics Committee (15/EE/0435) and is, therefore, part of the NIHR Clinical Research Network Portfolio. North West London Clinical research network are the lead network.

## TRIAL REGISTRATION

This trial is registered with the International Standard Randomised Controlled Trial Register (#ISRCTN37915093).

**RANDOMISATIONS**
To randomise, please email **mrcctu.stophcv1@ucl.ac.uk** or call the MRC CTU at UCL
(See Manual of Operations)
**RANDOMISATIONS SHOULD ONLY OCCUR ON DAYS WHEN DAY 3 VISITS CAN BE SCHEDULED IN CLINIC (see Table 8 P41).**

**SAE REPORTING**
Within 24 hours of becoming aware of an SAE, please email a completed SAE form to the MRC CTU at UCL at **mrcctu.stophcv1@ucl.ac.uk**
**Any CRFs sent by email must be encrypted or transferred using other secure methods**

## TRIAL ADMINISTRATION

Please direct all queries to the STOP-HCV-1 Trial Manager at the MRC Clinical Trials Unit at UCL in the first instance using mrcctu.stophcv1@ucl.ac.uk; clinical queries will be passed to the Chief Investigator via the Trial Manager.

### COORDINATING SITE

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# SUMMARY OF TRIAL

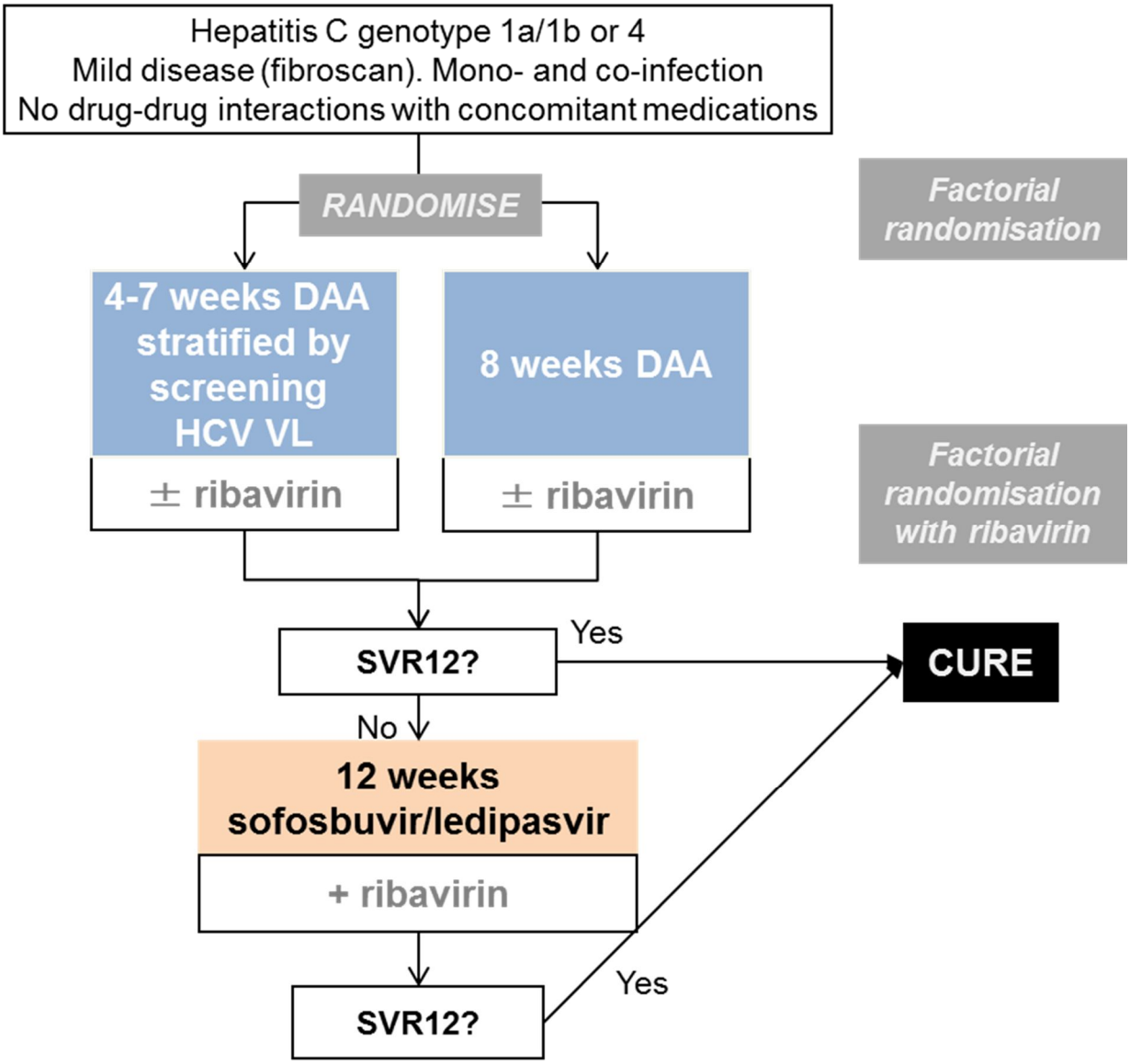
| SUMMARY INFORMATION TYPE | SUMMARY DETAILS |
|---|---|
| **Acronym** | STOP-HCV-1 |
| **Long Title of Trial** | Stratified Treatment OPtimisation for HCV-1 |
| **Version** | 7.0 |
| **Date** | 21-Feb-2018 |
| **ISRCTN #** | ISRCTN37915093 |
| **EudraCT #** | 2015-005004-28 |
| **CTA #** | 19174/0370/001-0001 |
| **MREC #** | 15/EE/0435 |
| **Study Design** | An open-label randomised controlled trial (RCT) testing biomarker-stratified short-course first-line and re-treatment direct-acting antiviral (DAA) oral treatment regimens to cure mild chronic Hepatitis C (HCV) disease. |
| **Type of Patients to be Studied** | Adults (≥18 years) infected with HCV genotype 1a/1b or 4 for ≥6 months, with detectable plasma HCV RNA and mild liver disease (Fibroscan score F0-F1 or biopsy proven minimal fibrosis), HCV viral load <10 million IU/ml, no previous DAA exposure (previous pegylated-interferon/ribavirin allowed) and not pregnant. Patients co-infected with HIV are eligible if HIV viral load has been <50 copies/ml for >24 weeks on anti-HIV drugs. |
| **Setting** | NHS |
| **Interventions to be Compared** | The main intervention to be compared is varying (intervention) 4-7 weeks vs fixed (control) 8 weeks combination first-line DAA treatment, with or without ribavirin, in an open-label partial factorial design.<br>• Varying intervention duration will be stratified by baseline HCV RNA on a sliding scale, with duration determined by estimated time for HCV RNA to decline to reduce levels to ~1 copy in the whole body at end of treatment.<br>• As soon as viral failure is detected at any time post-randomisation (first-line failure), patients will stop first-line treatment (if still receiving it) and be immediately retreated with 12 weeks of a different regimen.<br>• Ribavirin will be dosed twice daily, adjusted for weight<br>Current first-line combination regimens are those licenced for use against Hepatitis C, namely:<br>(i) a fixed dose combination of DAA active against genotype 1a/1b and 4; the Abbvie combination ombitasvir/paritaprevir/ritonavir (12.5mg/75mg/50mg) co-formulated film-coated tablets once daily (total daily dosage: 25/150/100mg) plus for genotype 1a/1b one dasabuvir 250 |

| SUMMARY INFORMATION TYPE | SUMMARY DETAILS |
|---|---|
| | mg tablet twice daily (total daily dosage: 500mg) (using "ombitasvir/paritaprevir/(dasabuvir)/ritonavir" to denote the combination regimen)<br>(ii) a fixed dose combination of 2 novel DAA active against all genotypes; the Abbvie combination glecaprevir/pibrentasvir (100mg/40mg) co-formulated tablets once daily (total daily dosage: 300/120mg)<br>Current retreatment regimens are:<br>(iii) a fixed dose double combination of sofosbuvir/ledipasvir (400mg/90mg) once a day plus ribavirin twice a day |
| **Study Hypotheses** | **(i)** HCV-RNA determined short-course (4-7 weeks) first-line will cure similar proportions with chronic, mild HCV disease as a fixed 8 week first-line course once failures have been retreated for 12 weeks<br>(ii) Adjunctive ribavirin improves cure rates with biomarker-stratified short-course and fixed duration DAA first-line regimens that are shorter than the full licensed duration of therapy<br>(iii) Re-treatment with a longer 12 week regimen, given after detecting virological failure on or following first-line treatment, still achieve cures in the majority of the small proportion of patients failing first-line treatment. |
| **Primary Outcome Measure** | For the varying duration comparison the primary outcome will be:<br>▪ Sustained Virological Response (SVR, plasma HCV RNA persistently <LLOQ (lower limit of quantification)) measured 12 weeks after the end of the combined first and any re-treatment phases (SVR12)<br>For the ribavirin comparison the primary outcome will be:<br>▪ SVR12 after first-line treatment only |
| **Secondary Outcome Measure(s)** | ▪ SVR12 after first-line treatment (where not the primary outcome)<br>▪ SVR12 after the end of the combined first and any re-treatment phases (where not the primary outcome)<br>▪ SVR24 after the end of the combined first and any re-treatment phases<br>▪ SVR24 after first-line treatment only<br>▪ lack of initial virological response<br>▪ viral load rebound after becoming undetectable<br>▪ serious adverse events<br>▪ grade 3/4 adverse events<br>▪ grade 3/4 adverse events judged definitely/probably related to interventions<br>▪ treatment-modifying adverse events (any grade)<br>▪ grade 3/4 anaemia<br>▪ emergence of resistance-associated HCV variants<br>▪ sensitivity/specificity of point–of-care diagnostic for IL28<br>▪ costs and cost-effectiveness |
| **Randomisation** | Patients will be allocated 1:1 using a factorial design to each of |

| SUMMARY INFORMATION TYPE | SUMMARY DETAILS |
|---|---|
| | • biomarker-stratified varying vs fixed duration<br>• adjunctive ribavirin or not (this randomisation will be a partial factorial in those receiving a shorter course than the full licensed duration of therapy)<br>Randomisation will be stratified. |
| **Number of Patients to be Studied** | 408 |
| **Duration** | ▪ Patients are planned to be recruited over 2 years<br>▪ Each first-line intervention will be administered for 4-8 weeks<br>▪ Each patient will be followed for 24 weeks post end of first-line treatment: if they fail first-line, they will receive another 12 weeks re-treatment and be followed for a further 24 weeks post end of re-treatment<br>▪ The overall trial duration is planned for 4 years (including start-up and close-out) |
| **Sponsor** | Imperial College London |
| **Funder** | Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership (14/02/17) |
| **Trial Manager** | Emily Dennis |
| **Chief Investigator** | Graham Cooke |
| **MRC CTU at UCL Project Leader** | Ann Sarah Walker |

## TRIAL SCHEMA

**Figure 1**




**Follow-up:** day 3, 7, 14, 28, End of Treatment; then 4-weekly until 12 weeks post end of treatment, then at 24 weeks post end of treatment.

**Primary endpoint: SVR12 (ie cure)**

**Secondary endpoints**: SVR24; lack of initial virological response; viral load rebound (**relapse**) after becoming undetectable; serious adverse events; grade 3 or 4 adverse events; grade 3 or 4 adverse events judged definitely/probably related to the intervention; treatment-modifying adverse events of any grade; grade 3 or 4 anaemia; emergence of resistance-associated Hepatitis C variants

Note: as above, the ribavirin randomisation will be a partial factorial in those receiving a shorter course than the full licensed duration of therapy.

# TRIAL ASSESSMENT SCHEDULE

**Table 1 Trial Assessment Schedule – first-line treatment real-time tests (see Table 2 for first-line sample storage)**

| | | DAY POST RANDOMISATION* | | | | | EOT | WEEK POST EOT | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | SCREENING† | 0 | 3 | 7 | 14 | 28 | | 4 | 8 | 12 | 24 |
| Control: 8 weeks treatment [continuing] | | DAA | [DAA] | [DAA] | [DAA] | DAA | | *(see retreatment schedule below for any treatment after first-line EOT)* | | | |
| Intervention maximum: 7 weeks treatment [continuing] | | DAA | [DAA] | [DAA] | [DAA] | DAA | | | | | |
| Intervention minimum: 4 weeks treatment [continuing] | | DAA | [DAA] | [DAA] | [DAA] | DAA | | | | | |
| Eligibility assessment | X | | | | | | | | | | |
| Patient information sheet and consent | X | | | | | | | | | | |
| Randomisation | | X | | | | | | | | | |
| Clinical assessment[(a)] | | X | X | X | X | X | X | X | X | X | X |
| Self-reported adherence | | | X | X | X | X | X | | | | |
| Fibroscan or biopsy** | (X) | | | | | | | | | | |
| Weight (kg) | X | | | | | X | X | X | | X | X |
| Height (m) | X | | | | | | | | | | |
| Urine pregnancy test if child-bearing potential | | X | | | | X | X | | | X | X |
| Quality of life[(b)] | | X | | | | | X | | | X | |
| EDTA blood for haematology[(c,h,i)] (5ml) | (X) | X | | | X | X | X | | | X | X |
| Clotted blood for biochemistry[(d,h,i)] (5ml) | (X) | X | | | X | X | X | | | X | X |
| Coagulation markers (2.5ml) | (X) | | | | | | | | | | |
| Real-time HCV viral load[(h,i)] (10ml) | (X) | X | X | X | X | X | X | X | X | X | X |
| Point of care IL28 polymorphism test (Epistem)[(e, g)] | | X | | | | | | | | | |
| Total blood draw in ml for real-time tests | - | 20 | 10 | 10 | 20 | 22.5 | 22.5 | 10 | 10 | 22.5 | 22.5 |
| **If HIV-infected** - HIV viral load (9ml)<br>(additional) - CD4 cell count [(f)] | (X)<br>(X) | | | | | | X<br>(X) | | | | X<br>(X) |

() indicate tests that will have already been performed as part of standard management, but results will be recorded for the trial. Screening blood tests should have been performed within 60 days prior to randomisation.

On treatment visits should be within ±1 day of the nominal visit day and end of treatment (EOT) visits within ±3 days of the nominal visit day. The Day 3 visit must occur 3 or more calendar days before the Day 7 visit (that is, there should be two calendar days completely separating them). Any patient with a single HCV RNA >lower level of quantification (LLOQ) after two consecutive HCV RNA <LLOQ, or with a single value >2000 IU/ml and >1 log10 increase above the HCV RNA nadir on treatment or post EOT should be recalled for a second HCV RNA test at least one week after the initial value to confirm whether or not failure has occurred (See **Section 5.2** p43). Quality of life should also be assessed at this confirmation of failure visit.

* If a patient fails at any time point from day 14, then they move to the flow sheet for re-treatment below. See **Section 5.2** (p43) for definitions of failure

† Screening visit may be any time up to 60 days prior to randomisation, since patients with mild disease will be stable.

** Fibroscan or biopsy may be conducted within 180 days of randomisation

(a) Including record of concomitant medications, grade 3 or 4 or serious adverse events, adverse events (including reactions) of any grade leading to treatment modification including interruption/early discontinuation, resource utilisation, pill count.

(b) Quality of life will be assessed using the EuroQol (5 dimensions) (EQ-5D), the Medical Outcomes Study Short-Form 12 Item Survey[1] (SF-12, version 2) and the Cognitive Function Scale[2] (MOSCOG). Quality of life should also be performed at any additional visits to confirm HCV viral load failure.

(c) For real-time measurement of haemoglobin, white cell count, lymphocytes, neutrophils, platelets.

(d) For real-time measurement of alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin, albumin and creatinine, and calculation of creatinine clearance (Cockcroft Gault).

(e) Only with specific consent for genetic testing.

(f) Screening CD4 cell count from within 1 year of randomisation can be used.

(g) EPISTEM test can be done at any time point if not possible on day 0.

(h) If a participant is hard to bleed, the blood tests should be prioritised as follows: Biochemistry>haematology (FBC>differential)>HCV viral load >storage.

(i) If unable to bleed on day 28, EOT or post-EOT week 12, the patient should be recalled, as these are critical visits for clinical care.

**Table 2 Sample Collection Schedule – first-line treatment sample storage**

| | DAY POST RANDOMISATION* | | | | | EOT | WEEK POST EOT | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 3 | 7 | 14 | 28 | | 4 | 8 | 12 | 24 |
| Storage: sites processing all samples locally | | | | | | | | | | |
| EDTA plasma for local storage (20ml blood) | X | | | | | X | | | X | |
| EDTA plasma for local storage (10ml blood) | | X | X | X | X | | X | X | | X |
| EDTA whole blood for local DNA storage [a,b] (2.5ml) | X | | | | | | | | | |
| Whole blood in PAXgene blood RNA tube (Qiagen) [a] (2.5ml) | X | | | | | | | | | |
| Storage: PBMC (20ml) [c,d] | X | X | X | | | X | X | | | |
| Total storage sample blood draw in ml | 45 | 30 | 30 | 10 | 10 | 40 | 30 | 10 | 20 | 10 |
| Storage: sites sending key samples to Glasgow and able to retrieve remnant plasma from local laboratory if virological failure occurs | | | | | | | | | | |
| EDTA whole bloodfor DX to Glasgow (20ml blood) | X | | | | | | | | X | |
| EDTA whole blood for DX to Glasgow (10ml blood) | | X | X | X | | | X | | | |
| EDTA whole blood for DNA storage for DX to Glasgow [a, b] (2.5ml) | X | | | | | | | | | |
| Whole blood in PAXgene blood RNA tube (Qiagen) for DX to Glasgow [a] (2.5ml) | X | | | | | | | | | |
| Total storage sample blood draw in ml | 25 | 10 | 10 | 10 | 0 | 0 | 10 | 0 | 20 | 0 |
| Remnant plasma obtainable from local service laboratory on request from study team [e] | | | | | X | X | | X | | X |

(a) Only with specific consent for genetic testing.
(b) Can be taken at any time point if not possible on day 0.
(c) Only in a subset of sites with capacity to extract cells.
(d) If day 0 taken, up to a maximum of 4 other timepoints will be collected with EOT being most important. The collection on day 0 can be taken at either screening or day 0.
(e) These samples are most likely to be required from patients who experience virological failure.

Sites processing samples locally will initially store samples on site before shipping to a central location refer to the 'STOP-HCV-1 Laboratory – for Local Processing & Storage' for more details.
Sites sending (unprocessed) key samples to the HCV Research UK Biobank (at the MRC University of Glasgow Centre for Virus Research) should refer to the STOP HCV-1 Laboratory manual for sites sending STOP HCV-1 samples to HCV Research UK Biobank' for more details.

Samples may be shipped outside of the UK to North America or Europe for additional tests after the end of the trial

**Table 3 Trial Assessments and Sample Collection Schedule – Re-treatment**

| | START OF RE-TREATMENT (0) * | WEEKS FROM START OF RE-TREATMENT | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 2 | 4 | 8 | 12 (EOT) | 16 EOT+4 | 20 EOT+8 | 24 EOT+12 | 36 EOT+24 |
| 12 weeks treatment [continuing] | DAA | [DAA] | DAA | DAA | | | | | |
| Clinical assessment[a] | X | X | X | X | X | X | X | X | X |
| Self-reported adherence | | X | X | X | X | | | | |
| Weight (Kg) | X | | X | X | X | X | | X | X |
| Urine pregnancy test if child-bearing potential | X | | X | | X | | | X | X |
| Quality of life[b] | X | | | | X | | | X | |
| EDTA blood for haematology[c,g,h] (5ml) | (X) | X | X | X | X | | | X | X |
| Clotted blood for biochemistry [d,g,h] (5ml) | (X) | X | X | X | X | | | X | X |
| Coagulation markers[g] (2.5ml) | (X) | | | | | | | | |
| Real-time HCV viral load[g,h] (10ml) | (X) | X | X | X | X | X | X | X | X |
| Storage: sites processing all samples locally | | | | | | | | | |
| EDTA plasma for storage[g,h] (10ml blood) | (X) | X | X | X | X | X | X | X | X |
| Total blood draw in ml if storing locally | 32.5 | 30 | 32.5 | 30 | 32.5 | 20 | 20 | 32.5 | 32.5 |
| Storage: sites sending key samples to Glasgow and able to retrieve remnant plasma from local laboratory | | | | | | | | | |
| EDTA plasma for DX to Glasgow[g,h] (10ml blood) | (X) | | | | | | | X [e] | |
| Total blood draw in ml if not storing locally | 32.5 | 20 | 22.5 | 20 | 22.5 | 10 | 10 | 32.5 | 22.5 |
| Remnant plasma obtainable from local service laboratory on request from study team [f] | | X | X | X | X | X | X | | X |
| **If HIV-infected** - HIV viral load (9ml)<br>(additional) - CD4 cell count | X<br>(X) | | | | X<br>(X) | | | | X<br>(X) |

* If laboratory tests and plasma storage have already been performed in the prior 7 days as part of the first-line schedule above, then they do not need to be repeated at the start of re-treatment.

(a) Including record of concomitant medications, grade 3 or 4 or serious adverse events, adverse events of any grade leading to treatment modification including interruption/early discontinuation, resource utilisation, pill count;

(b) Quality of life will be assessed using the EuroQol (5 dimensions) (EQ-5D), the Medical Outcomes Study Short-Form 12 Item Survey[1] (SF-12, version 2) and the Cognitive Function Scale[2] (MOSCOG).
(c) For real-time measurement of haemoglobin, white cell count, lymphocytes, neutrophils, platelets
(d) For real-time measurement of alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin, albumin and creatinine, and calculation of creatinine clearance (Cockcroft Gault).
(e) For sites shipping unprocessed samples to the HCV Research UK Biobank, on the occasion a participant has a detectable HCV viral load at or after retreatment EOT, EOT +12 week storage sample should be taken, this sample however should not be sent to Glasgow, contact the STOP HCV-1 team for further shipment instructions.
(f) These samples are most likely to be required from patients who experience virological failure
(g) If a participant is hard to bleed, the blood tests should be prioritised as follows: Biochemistry>haematology (FBC>differential>INR)>HCV viral load >coagulation markers>storage.
(h) If unable to bleed on week 4, EOT or post-EOT week 12, the patient should be recalled, as these are critical visits for clinical care.

# CONTENTS

# ABBREVIATIONS

| Abbreviation | Expansion |
|---|---|
| AE | Adverse event |
| AR | Adverse reaction |
| ART | Antiretroviral therapy |
| ARV | Antiretroviral |
| BID | Bis in die (twice a day) |
| BNF | British National Formulary |
| CEAC | Cost effectiveness acceptability curve |
| CF | Consent Form |
| CI | Chief Investigator |
| CI | Confidence interval |
| CLRN | Comprehensive Local Research Network |
| COM | Clinical Operations Manager |
| CPM | Clinical Project Manager |
| CrCl | Creatinine clearance (Cockcroft Gault) |
| CRF | Case Report Form |
| CRN | Clinical Research Network |
| CTA | Clinical Trials Authorisation |
| CTIMP | Clinical trial of an investigational medicinal product |
| CTU | Clinical Trials Unit |
| DAA | Direct Acting Antiviral |
| DCF | Data Clarification Form |
| DH | Department of Health |
| DM | Data Manager |
| DMC | Data Monitoring Committee |
| DNA | Deoxyribonucleic acid |
| DPA | (UK) Data Protection Act |
| DSUR | Developmental Safety Update Report |
| ECRIN | European Clinical Research Infrastructure Network |
| EFGCP | European Forum for Good Clinical Practice |
| EMA | European Medicines Agency |
| EOT | End of Therapy |

| Abbreviation | Expansion |
|---|---|
| EU | European Union |
| EudraCT | European Union Drug Regulatory Agency Clinical Trial |
| EVR | Early virological response |
| FDA | (US) Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLE | Glecaprevir |
| G/P | Glecaprevir/Pibrentasvir |
| GP | General Practitioner |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| HRA | Health Research Authority |
| HRF | Health related finding |
| IB | Investigator Brochure |
| ICER | Incremental cost-effectiveness ratio |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IMP | Investigational medicinal product |
| INSTI | Integrase inhibitor |
| IRAS | Integrated Research Application System |
| ISRCTN | International Standard Randomised Controlled Trial Number |
| ITT | Intention-to-treat |
| LLOQ | Lower level of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MRC | Medical Research Council |
| MRC CTU at UCL | Medical Research Council Clinical Trials Unit at University College London |
| NHS | National Health Service |
| NIHR | National Institute for Health Research |
| NIHR CSP | National Institute for Health Research Co-ordinated System for gaining NHS Permission |
| NIMP | Non-investigational-medicinal product |
| NNRTI | Non-nucleoside reverse transcriptase inhibitor |
| NRTI | Nucleoside reverse transcriptase inhibitor |
| NRES | National Research Ethics Service |

| Abbreviation | Expansion |
|---|---|
| OD | Once daily |
| PGP | P-glycoprotein |
| PI | Principal Investigator |
| PI | Protease inhibitor |
| PIB | Pibrentasvir |
| PIS | Patient Information Sheet |
| PK | Pharmacokinetics |
| QALY | Quality-adjusted life year |
| QD | Quaque die (every day, ie once a day) |
| QMAG | Quality Management Advisory Group |
| QoL | Quality of life |
| QP | Qualified Person |
| R&D | Research and Development |
| RCT | Randomised controlled trial |
| REC | Research Ethics Committee |
| RGC | Research Governance Committee |
| RGF | Research Governance Framework (for Health and Social Care) |
| RNA | Ribonucleic acid |
| RTV (/r) | Ritonavir |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SAR | Serious adverse reaction |
| SD | Standard deviation |
| SMT | Senior Management Team |
| SOP | Standard operating procedure |
| SPC | Summary of Product Characteristics |
| SSA | Site-specific approval |
| SSI | Site-specific information |
| SUSAR | Suspected unexpected serious adverse reaction |
| SVR | Sustained virological response (persistently undetectable) |
| SVR12 | Sustained virological response (persistently undetectable) 12 weeks after EOT |
| SVR24 | Sustained virological response (persistently undetectable) 24 weeks after EOT |
| TDF | tenofovir disoproxil fumarate |

| Abbreviation | Expansion |
|---|---|
| TM | Trial Manager |
| TMF | Trial Master File |
| TMG | Trial Management Group |
| TMT | Trial Management Team |
| TSC | Trial Steering Committee |
| UAR | Unexpected adverse reaction |
| UKCRN | UK Clinical Research Network (now the NIHR CRN) |
| VL | Viral load |
| ZDV | Zidovudine |
| WHO | World Health Organization |
| WOCBP | woman of childbearing potential |

# 1 BACKGROUND

## 1.1 HEPATITIS C

Hepatitis C (HCV) is a major challenge to the United Kingdom (UK) both for the individual and for public health. There are an estimated 215,000-265,000 UK individuals living with HCV infection[3,4] and those chronically infected are at risk of severe liver diseases (cirrhosis, liver failure and hepatocellular carcinoma). Progression to end-stage liver disease is more rapid in those with other medical conditions, particularly HIV co-infection. Treatment of infected individuals has the additional potential to reduce ongoing transmission through needle use and sex, and from mother-to-child.

Morbidity and mortality from HCV are an increasing challenge to the NHS. Healthcare costs related to HCV are currently estimated to be £82.7m a year and productivity losses £184-367m a year[5]. HCV-related hospital admissions have risen from 612 in 1998 to 2268 in 2011, deaths have risen from 98 in 1996 to 381 in 2011 and the proportion of liver transplants undertaken due to HCV has risen steadily from 10% in 1996 to 18% in 2011.

Viral genotype is an important factor in determining both choice and duration of treatment with current therapeutic options. Globally, genotype 1 is the most common, accounting for approximately 46% of all infections, very close to UK estimates[6]. As the most common genotype in most well-resourced health economies, particularly the USA, genotype 1 has been the greatest focus of the initial development of new oral drugs. However, other genotypes also make a substantial contribution to the UK Hepatitis C burden.

Curative treatments have been available for hepatitis C for some time. However, as of early 2015, standard treatment for HCV infection still involved long courses (24-48 weeks), of relatively toxic therapy with relatively low chance of cure (40-50%). The nature of therapy remains a major barrier to uptake of treatment and hence control of the epidemic. A new generation of well-tolerated, oral, directly acting antivirals (DAAs) has transformed HCV treatment, with the potential to cure hepatitis C in most patients after 8-12 weeks of therapy. All HCV-infected adults with mild disease could, in theory, be cured with these regimens, substantially reducing future morbidity and mortality. For genotype 1, the first two interferon-free combination regimens approved were:

- A ritonavir-boosted triple combination of paritaprevir/r, ombitasvir (Viekirax®, Abbive, UK) and dasabuvir (Exviera®, Abbvie, UK)
- sofosbuvir/ledipasvir (Harvoni®, Gilead, USA).

The ritonavir-boosted combination of paritaprevir/r and ombitasvir (without dasabuvir) has also been approved for genotype 4 infection. Other regimens that are active against more, or even all, viral genotypes have also been approved or have been submitted for approval.

The new treatments for HCV offer the potential for curative therapy for the individual and the opportunity to break transmission pathways, leading to the real possibility of eliminating the HCV epidemic in the UK. A recent systematic review shows a clear benefit of HCV cure in improving health outcomes across a range of clinical settings[7], and there is no evidence to suggest that this differs according to the means used to achieve cure. However, there are several barriers to achieving this goal, one of the most important being the budget required. The new interferon-free treatments are very expensive, costing in excess of £3000 per week[8]. Based on current estimates of DAA drug costs, the drug budget alone for treating all UK patients (assuming successful first-line therapy in all cases) would be in excess of £2 billion. With a current annual NHS HCV treatment spend of £180m, ensuring treatment access for all is a major challenge. Beyond costs, more importantly even 8-12 weeks treatment will be challenging for many patients with HCV whose chaotic lifestyles are a

barrier to adhering to treatment. Treatment with shorter courses of treatment would potentially increase access to treatment for difficult to reach groups and could have an impact on onward transmission.

## 1.2 EXISTING RESEARCH

As above, the first two interferon-free combinations of treatment to be given European approval are paritaprevir/ombitasvir/ritonavir/dasabuvir (brand name Viekirax® and Exviera®, Abbvie, UK) (with or without ribavirin) and sofosbuvir/ledipasvir (brand Harvoni®, Gilead, USA).

Ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, is indicated for use as a treatment for chronic HCV genotype 1 infection in adults, regardless of fibrosis stage or treatment history (**Table 4**)[9,10]. The regimen is an all-oral, short-duration therapy that does not require co-administration with pegylated interferon. The regimen is the first approved treatment for chronic HCV to combine three DAAs with distinct mechanisms of action to target the virus at multiple steps in its lifecycle. This combination approach increases the likelihood of treatment success and reduces the chances of relapse after treatment. Moreover, the three DAAs have non-overlapping resistance profiles and as such have a high barrier to resistance when used in combination[11].

**Table 4 Characteristics of ombitasvir, paritaprevir, ritonavir, and dasabuvir**

| Parameter | Ombitasvir (25mg) | Paritaprevir (150 mg) | Ritonavir (100mg) | Dasabuvir (250 mg) |
|---|---|---|---|---|
| Drug class | NS5A inhibitor | NS3/4A protease inhibitor | Pharmacokinetic enhancer | Non-nucleoside NS5B polymerase inhibitor |
| In vitro antiviral activity against genotypes | 1a, 1b, 2a, 2b, 3a, 4a, 5a, 6a | 1a, 1b, 2a, 3a, 4a, 6a | n/a | 1a, 1b |
| Potency against genotype 1 | High | Moderate | n/a | Low |
| Resistance barrier | Low | Moderate | n/a | Low |

In total, over 3,000 genotype 1 patients and almost 200 non-genotype 1 patients from over 25 countries have completed Phase 2 or 3 clinical trial programmes to assess the efficacy and safety of ombitasvir/paritaprevir/r with or without dasabuvir (**Table 5**)[12-15].

Sofosbuvir (nucleoside NS5B polymerase inhibitor) and ledipasvir (NS5a inhibitor) are available as a co-formulated single daily tablet[16] approved for use in genotype 1 infection for both treatment naïve and experienced populations (12 weeks therapy). The ION-1/2/3 Phase III studies[17-19] consistently showed efficacy of >90% within both treatment naïve and treatment experienced genotype 1 patients.

The role of ribavirin remains to be defined in the era of interferon free therapy. In combination with pegylated interferon, adjunctive ribavirin improves SVR and is an important part of treatment[20]. The most common adverse event resulting from ribavirin co-administration is anaemia which may require dose reduction. However, with more potent combination therapy, including ombitasvir/paritaprevir/dasabuvir/ritonavir and sofosbuvir/ledipasvir given for 12 weeks, the role of ribavirin is less consistent (for example, see **Table 5** and reference [19]). Ribavirin is manufactured

generically and is relatively inexpensive. Given that shortened durations of therapy carry less toxicity, the role of ribavirin in shortened therapy remains to be defined.

**Table 5 Phase III trials of ombitasvir/paritaprevir/dasabuvir/ritonavir**

| Study reference | Study design | Patient characteristics | Intervention | SVR12, n(%) | VF or relapse, n(%) | D/C due to AE, n(%) |
|---|---|---|---|---|---|---|
| **SAPPHIRE-I**<br><br>(Feld, et al., 2014) | Multicentre, randomised, double-blind, placebo-controlled, Phase 3 | TN (GT1a and GT1b), no cirrhosis (n=631) | A3D + RBV 12wks (n=473) | GT1a: 307/322 (95.3%)<br><br>GT1b: 148/151 (98.0%) | GT1a: 7/322 (2.2%)<br><br>GT1b: 1/151 (0.7%) | 3/473 (0.6%) |
| **PEARL-III**<br><br>(Ferenci, et al., 2014) | Multicentre, randomised, double-blind, placebo-controlled, Phase 3 | TN (GT1b), no cirrhosis (n=419) | A3D + RBV 12wks (n=210) | 209/210 (99.5%) | 1/210 (0.5%) | 0 |
| | | | A3D alone 12wks (n=209) | 207/209 (99.0%) | 0 | 0 |
| **PEARL-IV**<br><br>(Ferenci, et al., 2014) | Multicentre, randomised, double-blind, placebo-controlled, Phase 3 | TN (GT1a), no cirrhosis (n=305) | A3D + RBV 12wks (n=100) | 97/100 (97.0%) | 2/100 (2.0%) | 0 |
| | | | A3D alone 12wks (n=205) | 185/205 (90.2%) | 16/205 (7.8%) | 2/205 (1.0%) |
| **SAPPHIRE-II**<br><br>(Zeuzem, et al., 2014) | Multicentre, randomised, double-blind, placebo-controlled, Phase 3 | TE (GT1a and GT1b), no cirrhosis (n=394) | A3D + RBV 12wks (n=297) | GT1a: 166/173 (96.0%)<br><br>GT1b: 119/123 (96.7%) | GT1a: 5/173 (2.9%)<br><br>GT1b: 2/123 (1.6%)<br><br>All PT-relapse | 3/297 (1.0%) |
| **PEARL-II**<br><br>(Andreone, et al., 2014) | Multicentre, open-label, Phase 3 | TE (GT1b), no cirrhosis (n=179) | A3D + RBV 12wks (n=88) | 85/88 (96.6%) | 0 | 2/88 (2.3%) |
| | | | A3D alone 12wks (n=91) | 91/91 (100.0%) | 0 | 0 |

Abbreviations: TN, Treatment-naive; TE, treatment-experienced; GT, genotype; A3D, ombitasvir/paritaprevir/ritonavir and dasabuvir; RBV, ribavirin; VF, virologic failure; D/C, discontinued; AE, adverse events; PT, previous treatment.

Glecaprevir/pibrentasvir (Maviret®) is a highly potent, pangenotypic direct-acting antiviral regimen with a high barrier to resistance that has recently received European approval and is indicated for the treatment of chronic hepatitis C virus infection in adults (**Table 6**).

**Table 6 Characteristics of glecaprevir and pibrentasvir**

| Parameter | Glecaprevir (100mg) | Pibrentasvir (40mg) |
|---|---|---|
| Drug class | NS3/4A protease inhibitor | NS5A inhibitor |
| In vitro antiviral activity against genotypes | 1a, 1b, 2a, 2b, 3a, 4a, 6a | 1a, 1b, 2a, 2b, 3a, 4a, 5a, 6a |
| Potency against genotype 1 | High | High |
| Resistance barrier | High | High |

The regimen is an all-oral, short-duration therapy. In total, over 800 genotype 1 and over 900 genotype 2-6 non-cirrhotic patients have completed Phase 2 or 3 clinical trial programmes to assess the efficacy and safety of this combination (Table 7). The standard dose of glecaprevir (300mg) and pibrentasvir (120mg) for 8-12 weeks has consistently resulted in high efficacy rates in treatment-naïve and treatment-experienced individuals (96-100% for non-genotype 3 and 92-97% for genotype 3). There have been very low rates of treatment discontinuation due to adverse events. The current licenced indication for mild HCV disease is 8 weeks without ribavirin. While the addition of ribavirin to standard doses of glecaprevir/pibrentasvir has not yet been assessed, the addition of ribavirin may be advantageous if treating for less than 8 weeks duration.

**Table 7 Phase 2/3 studies evaluating glecaprevir/pibrentasvir in non-cirrhotic patients**

| Reference | Design | Patient characteristics | Intervention | SVR12, n(%) | VF/relapse, n(%) | D/C due to AEs, n(%) |
|---|---|---|---|---|---|---|
| **ENDURANCE-1**<br>Zeuzem et al[21] | Multicentre, randomised, open-label phase 3 | TN and TE (GT1a and GT1b), no cirrhosis (n=703) | G/P (300mg/120) 8wks (n=351)<br>G/P( 300mg/120mg) 12wks (n-352) | 348/351 (99%)<br>351/352 (99.7%) | 1/351 (0.3%)<br>0/352 (0%) | 0/351 (0%)<br>0/352 (0%) |
| **SURVEYOR-1 Part 1 and 2**<br>Kwo et al[22] | Multicentre, open-label, phase 2 | TN and TE (GT1, GT4-GT6), no cirrhosis (n=147) | G/P (200mg/120mg) 12wks (n=40)<br>G/P (200mg/40mg) 12wks (n=39)<br>G/P (300mg/120mg) 8wks (n=34)<br>G/P (300mg/120mg) 12wks (n=34) | GT1: 40/40 (100%)<br>GT1: 38/39 (97%)<br>GT1: 33/34 (97%)<br>GT4-6: 34/34 (100%) | GT1: 0/40 (0%)<br>GT1: 1/39 (3%)<br>GT1: 0/34 (0%)<br>GT4-6: 0/34 (0%) | GT1: 0/40 (0%)<br>GT1: 0/39 (0%)<br>GT1: 0/34 (0%)<br>GT4-6: 0/34 (0%) |
| **ENDURANCE-2**<br>Kowdley et al[23] | Multicentre, randomised, double-blind, placebo-controlled, phase 3 | TN and TE (GT2), no cirrhosis (n=202) | G/P (300mg/120mg) 12wks (n=202) | GT2: 195/196 (99%) | GT2: 0/196 (0%) | GT2: 0/196 (0%) |
| **SURVEYOR-2 Part 1 and 2** | Multicentre, open-label, | TN and TE (GT2-3), no cirrhosis (n=133) | G/P | GT3 TN: 28/29 (97%) | GT3 TN: 0/29 (0%) | GT3 TN: 0/29 (0%) |

| Reference | Design | Patient characteristics | Intervention | SVR12, n(%) | VF/relapse, n(%) | D/C due to AEs, n(%) |
|---|---|---|---|---|---|---|
| Kwo et al[22] | phase 2 | | 8wks (n=29) G/P (300mg/120mg) 12wks (n=25)<br><br>G/P (200mg/120mg) 12wks (n=24)<br><br>G/P + RBV (200mg/120mg) 12wks (n=25)<br><br>G/P (200mg/40mg) 12wks (n=30) | GT2: 24/25 (96%) GT3: 28/30 (93%) GT3 TE: 22/24 (92%) GT2: 24/24 (100%) GT3: 28/30 (93%) GT2: 25/25 (100%) GT3: 29/31 (94%) GT3: 25/30 (83%) | GT2: 0/25 (0%) GT3: 1/30 (3%) GT3 TE: 2/24 (8%) GT2: 0/24 (0%) GT3: 2/30 (7%) GT2: 0/25 (0%) GT3: 1/31 (3%) GT3: 3/30 (10%) | GT2: 0/25 (0%) GT3: 0/30 (0%) GT3 TE: 0/24 (0%) GT2: 0/24 (0%) GT3: 0/30 (0%) GT2: 0/25 (0%) GT3: 1/31 (3%) GT3: 0/30 (0%) |
| **ENDURANCE-3**<br><br>Foster et al[24] | Randomised, non-inferiority, phase 3, G/P vs SOF/DCV | TN (G3), no cirrhosis (n=390) | G/P (300mg/120mg) 8wks (n=157) G/P (300mg/120mg) 12wks (n=233) | GT3: 149/157 (95%) GT3: 222/233 (95%) | GT3: 6/157 (4%) GT3: 4/233 (1.7%) | GT3: 0/157 (0%) GT3: 1/233 (0.4%) |
| **ENDURANCE-4**<br><br>Asselah et al[25] | Multicentre open-label, phase 3 | TN and TE (GT4-6), no cirrhosis (n=121) | G/P (300mg/121) | GT4: 75/76 (99%) GT5: 26/26 (100%) GT6: 19/19 (100%) | GT4-6: 0/121 (0%) | GT4-6: 3/121 (2.5%) |

Abbreviations: TN, Treatment-naive; TE, treatment-experienced; GT, genotype; G/P, glecaprevir/pibrentasvir; RBV, ribavirin; VF, virologic failure; D/C, discontinued; AE, adverse events.

## 1.3 SHORTENED DURATIONS OF THERAPY

It is clear from the limited number of Phase II studies exploring shortened durations of DAA therapy that a high proportion of individuals can be cured with treatment durations shorter than the 12 week courses for which licenses have been granted for ombitasvir/paritaprevir/ritonavir with or

without dasabuvir and sofusbuvir/lepidasvir, and the 8 week courses for which licences have been granted for glecaprevir/pibrentasvir. This means that many patients will be prescribed much more medication than they require to be cured, with unnecessary inconvenience and costs. Three key combinations where there has been limited investigation of shorter treatments are paritaprevir/ombitasvir/dasabuvir/ritonavir, sofosbuvir/ledipasvir and the combination of elbasvir/grazeoprevir for which market approval was obtained in 2016. Such studies have been relatively small as shorter duration therapies have not been pushed for approval by the originator companies. Overall cure rates with 8 weeks of ombitasvir/paritaprevir/dasabuvir/ritonavir were 88% (N=80)[26], 67% with 6 weeks of sofosbuvir/ledipasvir[19], 84% (N=31) with 6 weeks of grazeoprevir/elbasvir/sofosbuvir in non-cirrhotic genotype 1 infection[27] and 80% in HIV co-infected individuals receiving 8 weeks of grazeoprevir/elbasvir[28].

There are two important questions: first, is it possible to identify patients who will cure with shorter course treatments? And second, is it more effective, and cost-effective, to try to cure as many patients as possible with a shorter-duration of initial therapy, accepting that a proportion who do not cure initially will need re-treatment, on which they may or may not achieve cure? There have not been any studies to date looking at sequential (i.e. first-line, re-treatment) strategies for HCV treatment with new interferon-free combinations of treatment. However there have been studies looking at re-treatment with interferon-free therapy in those who failed DAA treatment in registration trials. In theory, resistance associated variants (RAVs) may emerge with shorter course treatment and impact the success of re-treatment. In registration trials such failures were rare, but RAVs have been described following failure of the ombitasvir/paritaprevir/dasabuvir/ritonavir combination in NS5a (including M28 A/T/V, Q30/E/K/R), NS5B (including S556G/R), and NS3/4A protease (including R155K, D168V)[29]. In studies to date, the presence of such RAVs has had only a small impact on the success of further re-treatment. Patients in the SYNERGY study[30] who failed treatment achieved 90% SVR12 when retreated with sofosbuvir/ledipasvir without ribavirin for 12 weeks[31], and non-cirrhotics failing 6 weeks sofosbuvir/ledipasvir achieved 80% SVR12 when retreated with sofosbuvir/ledipasvir for 24 weeks (N=41) [32]. In the latter study, emergent resistance associated variants (RAVs) were less likely to occur in those who received shorter courses of treatment, suggesting a potential advantage to shorter courses of therapy.

There is consistent evidence that quantitative HCV viral load (VL) is useful in determining the chances of achieving SVR12 from a number of Phase II/III studies of interferon free combinations. With 8 weeks ombitasvir/paritaprevir/dasabuvir/ritonavir treatment[26] treatment-naïve patients with HCV viral load <800,000 IU/ml achieved 100% SVR12 compared to 86% if >800,000 IU/ml. In the SYNERGY trial[33], HCV VL <600,000 IU/ml was associated with SVR12 of 87% from 4 weeks of therapy. In the C-SWIFT study of another investigational drug, MK5172/8472, the impact of viral load was seen most clearly with the shortest durations of therapy (SVR12 44% after 4 weeks treatment in those with HCV VL <6x $10^6$ compared to 17% in those with HCV VL >6x $10^6$ [27]).

The IL28B polymorphism has been identified as an independent predictor of treatment outcome in interferon based regimens, the presence of IL28T allele being associated with a poorer response to treatment[34]. With the advent of more potent interferon free therapies, the impact of IL28 on outcomes appears to be reduced (for example [18]). However, there is some evidence that in shorter durations of therapy, IL28 may still be helpful in predicting who will respond[27]. Access to diagnosis is one limiting factor in IL28 testing being a routine part of care and has led to the development of a novel point of care diagnostic[35] by a UK SME (Epistem, Manchester).

## 1.4 RATIONALE FOR STUDY

The very high cure rates achieved with 12 and 8 weeks DAA regimens raise the question: what is the minimum duration of treatment that can achieve cure in the majority of patients?[36] Minimising (effective) treatment duration is important for ensuring widest and equitable access to curative therapy across all patients (particularly those who will struggle to take medicine and require support) for the same fixed budget, and for minimising toxicity. However, it is likely that response to DAA treatment will depend on individual level characteristics, offering the opportunity to stratify short-course treatment. The best studied biomarker to stratify treatment duration is plasma HCV RNA (viral load). Based on mean (SD) baseline viral load levels and viral load declines in studies to date, and assuming at most a modest negative correlation between initial values and rates of decline, a "sliding scale" of 4-7 weeks combination DAA treatment (where the precise duration of treatment depends on the individual's pre-therapy HCV viral load) should reduce virus levels to <1 copy in the whole person. The question to be addressed in this protocol is whether such an HCV RNA-stratified DAA duration (13-50% shorter, i.e. 50-83% of the original length) followed by re-treatment for those failing initial treatment gives similar cure rates to longer fixed-duration (8 weeks) therapy followed by re-treatment, in individuals with mild chronic Hepatitis C disease. Biomarker-stratified short-course treatment would enable more patients to be cured within the same overall budget, and would also have benefits in terms of less potential toxicity and easier to adhere to regimens for patients. This is particularly important for HCV, where a substantial minority come from disadvantaged populations (drug users, homeless, prisoners).

In addition, the drug ribavirin was an essential component of previous interferon-based treatments: however, its role in DAA regimens is less clear, providing minimal additional benefit when added to more potent regimens. However, it is cheap, with less toxicity when given for short duration, and modest benefits could allow shorter DAA regimens to be used more effectively. The trial will therefore also test whether the addition of ribavirin is beneficial in short course treatment, using a partial factorial design in those receiving shorter than the full licensed duration of therapy. Specifically:

**Ombitasvir/paritaprevir/ritonavir with or without dasabuvir**
All participants randomised to varying duration DAA treatment with this DAA combination will be additionally factorially randomised to adjunctive ribavirin or not. The rationale for the factorial randomisation in both groups (fixed and varying duration) is that the '8 week' treatment arm still represents a shorter arm than standard-of-care.

**Glecaprevir/pibrentasvir**
All participants randomised to varying duration DAA treatment with this DAA combination will be additionally factorially randomised to adjunctive ribavirin or not. However, participants randomised to the 8 week treatment group will not be additionally randomised to adjunctive ribavirin or not, since 8 weeks of this combination without ribavirin is the licenced, standard-of-care indication for mild HCV.

At the time the trial was designed there were two licenced combination therapies available for genotype 1 patients, of which ombitasvir/paritaprevir/dasabuvir/ritonavir was used first-line (with an 8 week standard course duration) and sofosbuvir/ledipasvir as re-treatment (as a 12 week standard course, with ribavirin). *A priori* it is reasonable to assume that their ordering in first-line vs re-treatment would be similar, although no studies to date have addressed the question whether regimen sequencing impacts performance in terms of overall cure from biomarker-stratified shortened first-line plus re-treatment. Other new combinations, including those active against other genotypes, have now been licensed or are also expected to be licenced over the next year. To enable

data to be generated on other genotypes, of which genotype 4 is the next largest group in the UK, trial patients may alternatively be treated with

- ombitasvir/paritaprevir/ritonavir first-line if they are genotype 4, since this combination (without dasabuvir) is licenced for the treatment of genotype 4 (but not genotype 1) patients
- glecaprevir/pibrentasvir first-line (genotype 1a/1b or 4) (8 week standard course) (licensed in both these genotypes)

All trial patients will continue to receive sofosbuvir/ledipasvir as re-treatment (as a 12 week standard course, with ribavirin).

Lastly, the provision of re-treatment within the trial will generate important data to inform strategic use of DAAs in treatment pathways for the NHS. The scientific knowledge generated is likely to generalise to other new HCV DAAs, and the mechanistic insights gained (in collaboration with the STOP-HCV consortium involving most of the leading HCV scientists in the UK) into the role of initial viral load declines and viral quasi-species, human polymorphisms and immune responses, will inform development and evaluation of further treatment strategies, for example tailoring treatment duration based on on-treatment responses, ultimately improving outcomes across the NHS.

## 1.5 RESEARCH OBJECTIVES

The overarching aim is to evaluate the efficacy of biomarker-stratified treatment of HCV and of adjunctive ribavirin with combination DAAs. This will allow identification of patients with minimal fibrosis and chronic HCV Hepatitis C infection who can be offered a high probability of cure with shortened courses of interferon-free, all oral DAA regimens. Such stratification will reduce cost-per-cure and improve access to those unable to adhere to 8-12 weeks of treatment.

The specific primary objectives are therefore:

- To test whether biomarker-stratified short-course HCV first-line treatment followed by 12 weeks re-treatment of those failing therapy is non-inferior to a fixed duration of 8 weeks first-line treatment followed by 12 weeks re-treatment of those failing therapy, in terms of overall HCV cure in patients with minimal fibrosis and chronic genotype 1 or 4 HCV infection.
- To test the benefits and risks of adding adjunctive ribavirin with 4-8 weeks first-line therapy.

The different strategies above will be tested using ombitasvir/paritaprevir/dasabuvir/ritonavir (genotype 1) or ombitasvir/paritaprevir/ ritonavir (genotype 4) or glecaprevir/pibrentasvir (genotype 1, 4) first-line, and sofosbuvir/ledipasvir/ribavirin re-treatment (genotypes 1, 4).

Secondary objectives are

- To test whether **first-line** biomarker-stratified 4-7 weeks first-line treatment is non-inferior to fixed duration 8 weeks first-line treatment in mild HCV infection (ie excluding re-treatment responses).
- To test whether re-treatment with 12 weeks of an alternative combination regimen, given after detecting virological failure on first-line treatment, still achieves cure in the majority of the small proportion failing short-course first-line.
- To explore whether factors other than baseline HCV viral load influence, and therefore could better predict, the response to (a) short course DAA treatment and (b) re-treatment. Factors explored will include viral factors such as minority resistance variants and viral diversity, initial virological response; host factors such as age, body mass index and human genetic variation (notably IL28 polymorphisms); and immune factors such as immune phenotyping before and

after treatment initiation. Mechanistic work will be embedded in the MRC HCV Stratified Medicine Consortium.

- To validate the performance of a novel point of care device for detecting IL28B polymorphism

## 1.6 RISKS AND BENEFITS AT PATIENT AND SOCIETAL LEVEL

The primary benefit of participation for individual patients is that >95% of individuals will achieve cure of hepatitis C without interferon-based treatment. For many, interferon will have been a barrier to accessing and/or adhering to treatment previously. Barriers to accessing treatment are likely to remain even with DAAs, as demand for treatment is expected to exceed the capacity to deliver it. For the majority of patients, we also expect that cure will be achieved with a shorter duration of therapy than they would have received through routine care. The primary outcome measure (sustained virological response 12 weeks after end of treatment, SVR12) has been associated with significant reductions in all-cause mortality, cirrhosis and liver cancer[37], and so achieving cure will significantly reduce individual patient's future risks of these events, whichever group they are randomised to. The study will provide access to medications that are now recommended as part of the WHO Essential Medicines list.

The main risk in participation is that short-course therapy will not lead to successful first-line treatment. In a recent study of shortened therapy (C-SWIFT) no treatment option was provided for those failing shortened therapy[38]. This was justified on the basis that those with mild disease had lower short-term risk of disease progression. Within this protocol, we will directly test a strategy of retreating patients failing short-course first-line therapy with 12 weeks of an alternative interferon-free treatment regimen. The evidence to date suggests that even in the presence of viral resistance mutations the success of re-treatment will be high and that the overall cure rate of patients will be >95% regardless of first-line regimen, duration of first-line treatment or use of adjunctive ribavirin Whilst clearly we plan to assess impact of short-course therapy on first-line cure rates, following the recommendation of EME, our primary endpoint is overall cure after first-line and re-treatment, since this overall cure is the most relevant endpoint for patients.

For any patients not cured by this strategy there are other licensed DAAs that have the potential to therapy in the future. These include, but are not limited to, sofosbuvir/velpatasvir (Gilead), elbasvir/grazoprevir (Merck).

The intervention agents used within this trial have completed Phase III trials and been approved by FDA and EMA relatively recently and have been provisionally recommended for use by NICE. There are data on adverse event profiles from over 3000 individuals with each of the intervention treatments in this study and no major safety/toxicity concerns have yet emerged (see **Sections 5.3 and 5.4**); as such, given the future mortality and morbidity, the potential for cure outweighs the risks of treatment for individuals. Because these medications are now being rolled out more widely, it is possible that new evidence of toxicity will emerge, but given that treatment has a finite duration, and the trial will test biomarker-stratified shortened courses, the likelihood of new toxicities emerging to place individual patients at unacceptable risk is low.

Other risks include the use of ribavirin (see **Section 5.6**). Ribavirin is a Category X drug in pregnancy[39]. Hence, women of child-bearing potential must avoid pregnancy for the duration of the study and for ≥4 months after ribavirin exposure[39]. Male patients must avoid pregnancy in their female partners for ≥7 months after ribavirin exposure because of the prolonged negative impact on normal spermatogenesis seen in animal models. Pregnancies that occur during the trial, either in a patient or in a female partner of a male patient (with their specific consent) will be reported as a

serious adverse event (SAE) (**Section 7**) during the active phase of follow-up (see **Section 7.2.1**). All female patients will be followed for at least 4 months (16 weeks) as part of the trial follow-up schedule (to 24 weeks post end of treatment (EOT)). Pregnancies in the female partners of male patients will be ascertained at this EOT+24 week visit (after both first-line and any necessary re-treatment) and at the patient's next routine clinic visit outside the trial (to cover the 7 month cut-off for ribavirin exposure in male patients). Information on pregnancy outcome will be reported to the MHRA. Although it is unknown to what extent ribavirin is excreted in breast milk, the Summary of Product Characteristics (SPC) recommends avoiding breast-feeding during ribavirin receipt.

Societal benefits arising from the study are potentially very substantial. The treatment interventions within this study are currently priced at a level where access will not be affordable for all infected patients. The findings from this study will inform how the UK can efficiently provide treatment to those with mild disease, avoid over-treating many patients and allow more patients to be cured within a finite resource. Furthermore, the findings will inform the more precise use of new treatments in patients for whom a 8-12 week course of therapy will still be challenging and will inform strategies that will allow individuals who may be cured with as little as 4 weeks of treatment to be identified.

# 2 SELECTION OF SITES/CLINICIANS

The trial Sponsor has overall responsibility for site and investigator selection.

## 2.1 SITE/INVESTIGATOR INCLUSION CRITERIA

Potentially eligible sites are those linked to NHS Operational Delivery Networks for hepatitis in England or similar structures in Scotland and Wales. Sites that are compliant with the inclusion criteria, and not excluded on the basis of exclusion criteria will be provided with a copy of this protocol, a trial summary and the Summary of Product Characteristics (SPC).

To participate in the STOP-HCV-1 trial, investigators and clinical trial sites must fulfil a set of basic criteria that have been agreed by the STOP-HCV-1 Trial Management Group (TMG) and are defined below.

Sites where a previous serious protocol breach has occurred in a trial co-ordinated by the MRC CTU at UCL will be visited and thoroughly reviewed before allowing patients to enter the trial.

Those centres that meet the criteria will be issued with the STOP-HCV-1 master file documentation for their Site-specific Approval (SSA) and MRC CTU at UCL accreditation documents. Centres must complete the STOP-HCV-1 Accreditation Form at the same time as applying for their SSA.

### 2.1.1 PI'S QUALIFICATIONS & AGREEMENTS

1. The investigators should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up-to-date curriculum vitae and other relevant documentation requested by the Sponsor, the REC and/or the regulatory authority.

2. The investigator should be thoroughly familiar with the treatment of HCV and the appropriate use of the investigational product(s) as described in the protocol and the SPC.

3. The investigator should be aware of, and should comply with, the principles of GCP and the applicable regulatory requirements. A record of GCP training should be accessible for all investigators.

4. The investigator and site should permit monitoring and auditing by the Sponsor and the MRC CTU at UCL (as delegated) and inspection by the appropriate regulatory authority.

5. The investigator should maintain a delegation log of appropriately-qualified persons to whom the investigator has delegated significant trial-related duties.

6. The investigator should sign an Investigator Statement, which verifies that the site is willing and able to comply with the requirements of the trial.

### 2.1.2 ADEQUATE RESOURCES

**1.** The investigator should be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period (that is, the investigator regularly treats the target population).

2. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

3. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

5. The site should have sufficient data management resources to allow prompt data return to the MRC CTU at UCL (refer to the Data Management Plan for timelines). Sites that have previously participated in MRC CTU-coordinated trials should have a proven track record of good data return.

### 2.1.3 SITE ASSESSMENT

Each selected clinical trial site must complete the STOP-HCV-1 Accreditation Form, which includes the Investigator Statement, Signature and Delegation of Responsibilities Log, and staff contact details. The Investigator Statement verifies that the site is willing, and able to comply with the requirements of the trial. This will be signed by the Principal Investigator at the site. In addition and in compliance with the principles of GCP, all site staff participating in the trial must complete the Signature and Delegation of Responsibilities Log and forward this to the MRC CTU at UCL. The MRC CTU at UCL must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Trial Master File (TMF) at the site and also at the MRC CTU at UCL.

## 2.2 SITE EXCLUSION CRITERIA

Sites will be excluded for the following reasons:

1. Competing studies that would impact on the ability to enrol quickly.

2. Slow turnaround of HCV viral load tests (>7 days for results).

3. No ability to provide 24 hour cover for trial patients.

4. Local governance approval likely to take >3 months.

5. Poor track record in terms of quality (retention in trials and quality of data returned) as judged by prior participation in MRC CTU trials and/or the STOP HCV Consortium.

## 2.3 APPROVAL AND ACTIVATION

The Clinical Trial Authorisation (CTA) for the trial requires that the Medicines and Healthcare Products Regulatory Agency (MHRA) be supplied with the names and addresses of all participating site principal investigators. Trial staff at the MRC CTU at UCL will perform this task; hence it is vital to receive full contact details for all investigators prior to their entering patients.

On receipt of the above documents at the MRC CTU at UCL, written confirmation will be sent to the PI. A Randomisation Pack will be provided to the site. The site pharmacist will also be informed of the site's activation.

1. The site should conduct the trial in compliance with the protocol as agreed by the Sponsor and, if required, by the regulatory authority, and which was given favourable opinion by the REC.

2. The PI or delegate should document and explain any deviation from the approved protocol which has a real, not hypothetical, impact on patient safety or on the scientific integrity of the trial, and communicate this with the trial team at the MRC CTU at UCL, together with a corrective action plan as to how such deviations will be avoided in future.

A list of activated sites may be obtained from the Trial Manager.

# 3 SELECTION OF PATIENTS

**There will be no exceptions to eligibility requirements at the time of randomisation.** Questions about eligibility criteria should be addressed prior to attempting to randomise the patient– clarifications may be sought from the STOP-HCV-1 Trial Manager or Chief Investigator.

The eligibility criteria are the standards used to ensure that only medically appropriate patients are considered for this study. Patients not meeting the criteria should not join the study. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, **it is important that no exceptions be made to these criteria for admission to the study**.

Patients will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below. The target population is adults who have evidence of chronic infection with hepatitis C but have not yet developed evidence of complications of infection. Recruitment will take place from both hepatology and infectious disease services caring for chronic HCV infection in sites linked to NHS Operational Delivery Networks for hepatitis.

## 3.1 PATIENT INCLUSION CRITERIA

1. Aged ≥18 years
2. Infected with HCV genotype 1a or 1b or 4 with access to first-line treatment appropriate for their genotype (ombitasvir/paritaprevir/(dasabuvir)/ritonavir or glecaprevir/pibrentasvir)
3. At least one detectable viremia 6 months prior to randomisation (by quantitative HCV RNA, qualitative assay or HCV genotype), with no intervening undetectable results
4. Plasma HCV RNA >LLOQ at screening
5. No evidence of significant liver fibrosis resulting from any aetiology (defined as Fibroscan* score ≤7.1kPa, equivalent to F0-F1[40], within 180 days prior to planned randomisation or biopsy consistent with mild fibrosis (Ishak score <=2/6) within 180 days prior to planned randomisation)
6. BMI >=18kg/$m^2$
7. Laboratory tests: platelets >=60x$10^9$/l, haemoglobin >12g/dl (male) or >11g/dl (female), creatinine clearance (estimated using Cockcroft-Gault) >=60ml/min, international normalised ratio (INR) <1.5
8. Screening HCV viral load <10,000,000IU/ml
9. Written informed consent obtained from the patient.

If HIV infected, then an additional eligibility criteria is:

10. On antiretroviral therapy with HIV viral load <50 copies/ml for >24 weeks at the screening visit.

*Fibroscan must be a valid result (based on at least 10 readings) performed by an experienced (as evidenced by CV and/or training logs) technician and conducted as described in the Manual of Operations.

## 3.2 PATIENT EXCLUSION CRITERIA

1. Previous DAA exposure for this infection (previous treatment with pegylated-interferon and/or ribavirin allowed. DAA treatment for a previously cured infection allowed).
2. FEMALES ONLY: Lactating, or pregnant, or planning to become pregnant, or not willing to use effective contraception, during the study and for four months after last dose of study medication.
3. FEMALES ONLY: currently taking ethinyl-oestradiol-containing medicinal products such as those contained in most combined oral contraceptives or contraceptive vaginal rings.
4. MALES only: planning pregnancy with female partner, or not willing to use effective contraception, during the study and for seven months after last dose of study medication.
5. Malignancy within 5 years prior to screening
6. Any condition in the judgement of the investigator which might limit the patient's life expectancy
7. Currently receiving medication know to interact with study medication (ombitasvir, paritaprevir, dasabuvir, ritonavir, sofosbuvir, ledipasvir, ribavirin, glecaprevir, pibrentasvir; see relevant prescribing information[9,10,16,39], **Sections 5.3.4, 5.4.4, 5.5.4** and **5.6.4** below, and www.hep-druginteractions.org)
8. Disorder which may cause ongoing liver disease including, but not limited to, active hepatitis B, ongoing alcohol misuse
9. Any disorder which in the opinion of the investigator may have a significant negative impact on the ability of the patient to adhere to the trial regimen
10. Use of other investigational products within 60 days of screening
11. Known hypersensitivity to any active ingredient and/or excipients of the study medicines, namely Microcrystalline cellulose, **Lactose monohydrate**, Croscarmellose sodium, Magnesium stearate, Gelatine, Shellac, Propylene glycol, Polyethylene glycol, Ammonium hydroxide, Pregelatinised maize starch, Sodium starch glycolate (type A), Maize starch, Hypromellose, Talc, Ethylcellulose aqueous dispersion, Triacetin, Copovidone, Colloidal anhydrous silica, vitamin E (tocopherol) polyethlyene glycol succinate, sodium stearyl fumarate, Polyvinyl alcohol, Macrogol 3350, Sunset yellow FCF aluminium lake (E110), Colouring agent (E132), Titanium dioxide (E171), Yellow iron oxide (E172), Red iron oxide (E172), Black iron oxide (E172).
12. History of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months
13. Haemoglobinopathies (e.g., thalassemia, sickle-cell anaemia).

## 3.3 NUMBER OF PATIENTS

408 patients will be (factorially) randomised to both varying vs fixed duration treatment, and adjunctive ribavirin or not (partial factorial).

The trial's ability to assess its primary question regarding biomarker-stratified treatment duration will be impaired if the vast majority of patients are enrolled with HCV VLs such that either they automatically receive 7 weeks treatment or 4 weeks treatment (see **Table 12**). The trial overall will

therefore recruit no more than one-third of patients who would be in the lowest treatment duration strata (if randomised to intervention), and no more than one third of patients who would be in the highest treatment duration strata (if randomised to intervention).

Although patients with mono- and HIV co-infection respond equally well to oral DAAs, the vast majority of HIV-HCV-co-infected patients in the UK are men. To ensure that trial results are generalizable to men and women, and mono- and co-infected individuals, the trial will therefore recruit no more than one-half of patients with HIV-coinfection.

## 3.4 CO-ENROLMENT GUIDELINES

Treatment with any other investigational product within 60 days prior to screening is an exclusion criteria, and therefore co-enrolment with a previous investigational medicinal product (IMP) trial will generally not be allowed, unless the patient is in a follow-up phase. Before enrolment into STOP-HCV-1 of a patient already participating in a previous trial (not of an investigational product), the site investigator must confirm with the investigators of the previous trial that co-enrolment is allowed. Co-enrolment of patients already participating in an observational study (eg the STOP-HCV cohort) is allowed.

Co-enrolment in future trials after the patient has been randomised within STOP-HCV-1 is considered in **Section 4.3**.

## 3.5 SCREENING PROCEDURES & PRE-RANDOMISATION INVESTIGATIONS

As patients with mild chronic HCV disease are relatively stable, a screening visit may be conducted within 60 days of randomisation, and fibroscan or biopsy may be conducted at any point within the 180 days preceding randomisation. The screening visit may be conducted at any time up to the day before randomisation, providing that results of blood tests to confirm eligibility in terms of laboratory abnormalities and HCV VL are available.

Written informed consent to enter into the trial and be randomised must be obtained from patients after explanation of the aims, methods, benefits and potential hazards of the trial and BEFORE any trial-specific procedures are performed or any blood is taken for the trial (see Consent Form).

It must be made completely and unambiguously clear that the patient is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

Signed consent forms must be kept by the investigator and documented in the case record forms (CRF) held at site and a copy given to the patient. With consent, a letter should be sent to the general practitioner informing him/her of the trial and the patient's involvement in it.

Separate consent will be sought for additional screening samples to explore host genomics affecting response to short course DAA, the impact of baseline putative viral resistance mutations and the role of immune responses in curing infection.

## 3.6 CONTRACEPTION

All trial participants must be willing to use effective contraception during the trial and for at least four (women) or seven (men) months after the last dose of trial medication, if they are either a woman of childbearing potential (WOCBP) or the fertile partner of a WOCBP. A WOCBP is defined as a woman who is fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Effective contraceptive methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal oral, intravaginal or transdermal contraception associated with inhibition of ovulation **unless** this contains ethinyl-oestradiol which is an exclusion criteria, see above.
- progestogen-only hormonal oral, injectable or implantable,contraception associated with inhibition of ovulation **unless** this contains ethinyl-oestradiol which is an exclusion criteria, see above
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence where this involves refraining from heterosexual intercourse during the entire period of risk. For sexual abstinence to be acceptable as an effective contraception abstinence must be specified as the preferred and usual lifestyle of the patient.

Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

# 4 REGISTRATION & RANDOMISATION

Eligibility will be confirmed via the Screening CRF and patients randomised using a partial factorial design to

- open-label varying vs fixed duration first-line treatment (1:1)
- open-label adjunctive ribavirin or not (1:1) (not those receiving glecaprevir/pibrentasvir and randomised to fixed 8 weeks first-line treatment)

All patients will receive either first-line ombitasvir/paritaprevir/(dasabuvir)/ritonavir or glecaprevir/pibrentasvir (based on genotype and local availability of the different regimens), and sofosbuvir/ledipasvir/ribavirin re-treatment as necessary.

Randomisation will be computer-generated. Randomisation will be conducted through the MRC CTU at UCL (see Manual of Operations for details).

Randomisation may occur on any day of the week: however, because of the need to enable early kinetics of HCV RNA response to be determined at day 3 in all patients (because this could potentially improve treatment stratification in future), and the ±1 day visit window around early on-treatment visits, this places restrictions on which days of the week the Day 3 visit can occur (**Table 8**). Each site should only randomise patients on days of the week when it will be possible for the patient to attend a Day 3 visit within the prescribed window. Further the Day 3 visit should occur 3 or more calendar days before the Day 7 visit (that is, there should be two calendar days completely separating them). Further, if randomising patients on a Friday, then sites should ensure that patients are provided with staff contact details in case of any difficulties with the medication over the weekend.

**Table 8 Schema for randomisation and Day 3 and 7 visits**

| | M | T | W | Th | F | Sa | Su | M | T | W | Th | F | Sa | Su | M | T | W | Th | F | Sa |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Randomise Monday | R | | | D3 | | | | D7 | | | | | | | D 14 | | | | | |
| Randomise Tuesday | | R | | | D3 | | | | D7 | | | | | | | D 14 | | | | |
| Randomise Wednesday | | | R | | | D3 | | | | D7 | | | | | | | D 14 | | | |
| Randomise Thursday | | | | R | | | D3 | | | | D7 | | | | | | | D 14 | | |
| Randomise Friday | | | | | R | | | D3 | | | | D7 | | | | | | | D 14 | |

Note: grey shading shows allowed windows around visit days following the trial schedule (**Table 1** p10). Randomisation is day 0.

## 4.1 RANDOMISATION PRACTICALITIES

Before randomisation, the patient's eligibility should be confirmed by completing the Screening CRF. All blood test results must be available to confirm that the patient is eligible in terms of laboratory criteria (contraindications and HCV VL): these blood tests should have been performed within 60 days prior to randomisation. The Enrolment CRF should then be completed before randomisation (including clinical assessment and EQ-5D) and blood drawn for investigations (as summarised in **Table 1** p10) including point-of-care testing for polymorphisms in the IL28 gene (Epistem) (if additional consent is provided) and storage (including for extraction and storage of DNA and RNA

from each patient provided additional optional consent is obtained). Completing the Enrolment CRF **before** randomisation ensures that all baseline characteristics are recorded before knowledge of the randomised allocation.

The study doctor or nurse should then email **mrcctu.stophcv1@ucl.ac.uk** or telephone the MRC CTU at UCL for randomisation (see Manual of Operations for further details), and will receive a trial number for the patient, the allocated treatment regimen, and the follow-up schedule (which will depend on randomisation to fixed vs varying first-line treatment duration). **Treatment should start as soon as possible after randomisation and no later than 1 day after randomisation so that early viral kinetics can be estimated from the Day 3 and 7 visits (see schema below). If a patient is not able to start treatment on the day of randomisation or the day after, then randomisation should be delayed.**

Randomisation is considered Day 0.

Further details on the process of randomisation can be found in **Section 9.1**.

**RANDOMISATIONS**
To randomise, please email to **mrcctu.stophcv1@ucl.ac.uk** or call MRC CTU at UCL (see Manual of Operations for further details)
**RANDOMISATIONS SHOULD ONLY OCCUR ON DAYS WHEN DAY 3 VISITS CAN BE SCHEDULED IN CLINIC (SEE Table 8 P41)**.

## 4.2 RANDOMISATION CODES & UNBLINDING

All randomisations are open-label and therefore there are no unblinding procedures.

## 4.3 CO-ENROLMENT GUIDELINES POST-RANDOMISATION

Patients should not be co-enrolled into any other trial of an investigational medicinal product (IMP) after joining STOP-HCV-1 and during follow-up for STOP-HCV-1. They may be enrolled into observational studies at any time, or into other IMP trials not relating to HCV infection following completion of this study, according to the criteria of those studies.

# 5 TREATMENT OF PATIENTS

## 5.1 INTRODUCTION

Each patient will be randomised using a partial factorial design to one of each of

- open-label varying vs fixed duration first-line treatment (1:1)
- open-label adjunctive ribavirin or not (1:1) (not those receiving glecaprevir/pibrentasvir and randomised to fixed 8 weeks first-line treatment)

All patients will receive first-line ombitasvir/paritaprevir/(dasabuvir)/ritonavir or glecaprevir/pibrentasvir (based on genotype and local availability of the different regimens), and sofosbuvir/ledipasvir/ribavirin re-treatment as necessary.

Each intervention is open-label because it is infeasible to blind durations of five different drugs and measurement of treatment success will be based on objective laboratory biomarker.

All interventions have been associated with a favourable adverse event profile, and are oral regimens, and therefore substantial issues with compliance are not expected. Individuals with a high likelihood of non-compliance (current injecting drug use, significant uncontrolled psychiatric conditions) are not eligible. Compliance with prescribed medication will be measured by pill counts and self-report.

## 5.2 DEFINITION OF FAILURE ON FIRST-LINE TREATMENT AND MOVE TO RE-TREATMENT

Failure of first-line treatment is defined as

i. two consecutive measurements of HCV RNA > LLOQ (taken at least one week apart) after two consecutive visits with HCV RNA <LLOQ at any time, with the latter confirmatory measurement also being >2000 IU/ml or
ii. two consecutive measurements of HCV RNA (taken at least one week apart) that are >1 log10 increase above HCV RNA nadir on treatment and >2000 IU/ml at any time.

Therefore any patient with a single HCV RNA >LLOQ after 2 consecutive HCV RNA <LLOQ, or with a single value >2000 IU/ml and >1 log10 increase above the HCV RNA nadir on treatment should be recalled for a second HCV RNA test at least one week after the initial value to confirm whether or not failure has occurred.

Patients who fail on or after first-line treatment will be sequentially treated with 12 weeks of an alternative DAA regimen plus ribavirin as soon as possible (but taking into consideration the wishes of the patient). Current data suggest that a high proportion of those not achieving cure with short-course first-line treatment will still achieve cure with subsequent longer re-treatment despite the presence of viral mutations; that is, that there are few, if any, negative long-term consequences of failing short-course DAA treatment, particularly in those with mild disease and given numerous other DAA combinations currently being tested. This hypothesis will be tested within the trial.

## 5.3 OMBITASVIR/PARITAPREVIR/(DASABUVIR)/RITONAVIR

### 5.3.1 PRODUCT

Ombitasvir/paritaprevir/(dasabuvir)/ritonavir is a triple combination of 3 novel DAA active against hepatitis C genotype 1a/1b and 4 manufactured by Abbvie, namely ombitasvir/paritaprevir/ritonavir (12.5mg/75mg/50mg) co-formulated film-coated tablets once daily (total daily dosage: 25/150/100 mg) plus one dasabuvir 250 mg tablet twice daily (total daily dosage: 500 mg).

Ombitasvir/paritaprevir/(dasabuvir)/ritonavir is a dosed orally and BID i.e.

- morning: 2 tablets of ombitasvir 12.5mg/paritaprevir 75mg/ritonavir 50mg plus one 250mg tablet of dasabuvir **with food without regard to fat or calorie intake**;
- evening: 1 x 250mg tablet of dasabuvir **with food without regard to fat or calorie intake.**

Genotype 4 patients take only ombitasvir/paritaprevir/ritonavir following the licensing indication.

### 5.3.2 TREATMENT SCHEDULE

The duration of first-line ombitasvir/paritaprevir/(dasabuvir)/ritonavir treatment will be determined by the randomisation to varying versus fixed duration, as described in **Section 5.7** below.

### 5.3.3 DISPENSING

All drugs will be dispensed by the pharmacist in the site pharmacy. There are no special storage requirements for the drug. The ombitasvir/paritaprevir/ritonavir comes packaged as blister packs in containers of 56 tablets (4 inner cartons of 14 tablets each). The dasabuvir component comes in blister packs of 56 tablets, with 4 inner cartons of 14 tablets each. For patients receiving 8 weeks first-line, ombitasvir/paritaprevir/(dasabuvir)/ritonavir will be dispensed every 4 weeks. For patients randomised to varying first-line duration, 4 weeks will be dispensed at the enrolment visit: at the week 4 visit, the precise number of days of treatment remaining will be dispensed by dividing packages before labelling.

### 5.3.4 DRUG-DRUG INTERACTIONS

#### 5.3.4.A Ombitasvir/paritaprevir/ritonavir (Viekirax®)

This combination contains a potent pharmacoenhancer, ritonavir. The following concomitant medications are **absolutely contraindicated** during the study when a patient is receiving ombitasvir/paritaprevir/ritonavir. The main risk is that levels of the concomitant medication will become toxic, and many of the drugs below have a narrow therapeutic index:

> Alfuzosin; efavirenz; pimozide; rifampin; sildenafil (Revatio), when taken for pulmonary artery hypertension (PAH); St. John's wort; oral midazolam (Versed), or triazolam; birth control pills or patches - Lo Loestrin FE, Norinyl, Ortho Tri-Cyclen Lo, Ortho Evra, and others; hormone replacement therapy such as Fem HRT; a vaginal ring such as NuvaRing; cholesterol-lowering medicine - gemfibrozil, lovastatin, simvastatin (Zocor, Vytorin, Simcor); ergot medicine - dihydroergotamine, ergotamine, ergonovine, methylergonovine; or seizure medicine - carbamazepine, phenytoin, phenobarbital. Inhaled corticosteroids containing fluticasone or other glucocorticoids metabolised through CYP3A4, should not be used, as there is an increased risk of Cushing's syndrome and an Addisonian crisis when the inhaled/systemic corticosteroids and/or ritonavir are ceased.

There are a number of other medications that are relatively contraindicated and these are listed in SPC for the drug. See also www.hep-druginteractions.org.

In addition, the tablets contain the following excipients: copovidone, K value 28, vitamin E polyethylene glycol succinate, propylene glycol monolaurate Type I, sorbitan monolaurate, colloidal silicon dioxide/colloidal anhydrous silica, sodium stearyl fumarate, polyvinyl alcohol, polyethylene glycol 3350/macrogol 3350, talc, titanium dioxide, and iron oxide red. Hypersensitivity to any of these components is a contraindication to receipt.

#### 5.3.4.B Dasabuvir (Exviera®)

Co-administration of Exviera® with medicinal products that are **strong or moderate enzyme inducers** is expected to decrease dasabuvir plasma concentrations and reduce its therapeutic effect[10]. Examples of contraindicated inducers are carbamazepine, phenytoin, phenobarbital; efavirenz, nevirapine, etravirine; enzalutamide; mitotane; rifampicin; St. John's Wort (Hypericum perforatum).

Medicinal products that are **strong CYP2C8 inhibitors** may increase dasabuvir plasma concentrations and must not be co-administered with Exviera®. Examples of contraindicated CYP2C8 inhibitors include gemfibrozil.

There are a number of other medications that are relatively contraindicated and these are listed in SPC for the drug. See also www.hep-druginteractions.org.

In addition, the tablets contain the following excipients: microcrystalline cellulose (D50-100 um), microcrystalline cellulose (D50-50 um), lactose monohydrate, copovidone, croscarmellose sodium, colloidal silicon dioxide/anhydrous colloidal silica, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350/macrogol 3350, talc, and iron oxide yellow, iron oxide red and iron oxide black. Hypersensitivity to any of these components is a contraindication to receipt.

### 5.3.5 Dose Modifications, Interruptions & Discontinuations of ombitasvir/paritaprevir/(dasabuvir)/ritonavir

#### 5.3.5.A Hepatic impairment

If the patient develops symptomatic hepatitis, or remains asymptomatic but with ALT $\geq$ x 10 ULN and the investigator believes this could possibly be related to drug all HCV drugs should be ceased. Re-challenge must not occur until the case is discussed with the TMG. It is recommended that asymptomatic patients experiencing ≥5 x ULN elevations of ALT are monitored more closely with weekly ALT testing until resolution.

In a pooled analysis of ombitasvir/paritaprevir/(dasabuvir)/ritonavir taken with or without ribavirin, 1% experienced elevations of ALT >5xULN[9]. Most occurred early (mean time 20 days after start of treatment; range 8-57 days), were asymptomatic and resolved without any dose interruption. The strongest association was with being female on ethinyl-oestradiol containing contraception, hence the co-administration of contraception containing this form of hormone is contraindicated. Other oestrogens such as oestradiol or conjugated oestrogens were not associated with liver enzyme elevations.

#### 5.3.5.B Renal impairment

No dose adjustment of Viekirax® with or without dasabuvir is required for patients with mild, moderate, or severe renal impairment.

#### 5.3.5.C Overdose

In early phase studies the highest single dose administered to healthy volunteers was paritaprevir (400mg) with 100mg of ritonavir, and 350mg for ombitasvir. No adverse events (AE) were observed although transient elevations of bilirubin were seen. As per the SPC in the case of overdose, the patient should be observed for any AE and symptomatic treatment of any AE initiated.

The highest documented single dose of dasabuvir administered to healthy volunteers was 2g. No study drug-related adverse reactions or clinically significant laboratory abnormalities were observed. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

#### 5.3.5.D Stopping drug early

Discontinuation criteria for all regimens are considered in **Section 5.7.**

#### 5.3.5.E Missed doses

Patients should be instructed that if vomiting occurs **within 6** hours of dosing an additional dose of trial drug should be taken. If vomiting occurs more than 6 hours after dosing, no further dose is needed.

If a dose of trial drug is missed, the prescribed dose can be taken within 6 hours. If more than 6 hours have passed since the drug is usually taken, the missed dose should NOT be taken and the patient should take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose. Any doses missed during the treatment course should be taken at the end of the prescribed course.

## 5.4 SOFOSBUVIR/LEDIPASVIR (HARVONI®)

### 5.4.1 PRODUCT

The fixed dose combination of sofosbuvir 400mg/ledipasvir 90mg is taken once a day. Patients should be instructed to swallow the tablet whole with or without food. Due to the bitter taste, it is recommended that the film-coated tablet is not chewed or crushed.

### 5.4.2 TREATMENT SCHEDULE

The duration of sofosbuvir/ledipasvir re-treatment, following confirmed virological failure on ombitasvir/paritaprevir/(dasabuvir)/ritonavir or glecaprevir/pibrentasavir first-line treatment will be 12 weeks, together with adjunctive ribavirin.

### 5.4.3 DISPENSING

Sofosbuvir/ledipasvir will be dispensed by the pharmacist in the site pharmacy. There are no special storage requirements for the drug. Sofosbuvir/ledipasvir is packaged in bottles containing 28 film-coated tablets. For patients receiving 12 weeks re-treatment, sofosbuvir/ledipasvir will be dispensed every 4 weeks.

### 5.4.4 DRUG-DRUG INTERACTIONS

Sofosbuvir/ledipasvir must not be co-administered with the potent P-glycoprotein (PgP) inducers, rifampicin, rifabutin and rifapentine; St John's Wort or the antiepileptic drugs – carbamazepine, phenytoin, phenobarbitol, oxcarbazepine. Co-administration will lead to lower levels of the DAA with increased risk of HCV virological failure.

Rosuvastatin must not be coadministered with sofosbuvir/ledipasvir as there is a several fold increase in AUC for the former with greatly increased risk of rhabdomyolysis (via inhibition of OATP and BCRP); pravastatin must be used with caution, as there is also an increased risk of myopathy. Sofosbuvir/ledipasvir also increases the levels of tenofovir and this is especially true in the presence of a pharmacoenhancer such as ritonavir or cobicistat. While these pharmacoenhancers are contraindicated on study as part of an antiretroviral regimen (in those who are HIV-infected), even without ritonavir or cobicistat, levels of tenofovir can be increased; the clinical significance of this interaction is unknown, and monitoring renal function is recommended. See also www.hep-druginteractions.org.

In addition, the tablets contain the following excipients: Copovidone, Lactose monohydrate, Microcrystalline cellulose, Croscarmellose sodium, Colloidal anhydrous silica, Magnesium stearate, Polyvinyl alcohol, Titanium dioxide, Macrogol 3350, Talc, Sunset yellow FCF aluminium lake (E110). Hypersensitivity to any of these components is a contraindication to receipt.

### 5.4.5 DOSE MODIFICATIONS, INTERRUPTIONS & DISCONTINUATIONS

#### 5.4.5.A Hepatic impairment

No dose adjustment of sofosbuvir/ledipasvir is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh-Turcotte [CPT] class A, B or C).

#### 5.4.5.B Renal impairment

No dose adjustment of sofosbuvir/ledipasvir is required for patients with mild or moderate renal impairment. The safety of sofosbuvir/ledipasvir has not been assessed in patients with severe renal impairment (estimated creatinine clearance <30 ml/min/1.73 $m^2$) or end-stage renal disease requiring haemodialysis. When sofosbuvir/ledipasvir is used in combination with ribavirin, see also **Section 5.6.5** below and the SPC for ribavirin for patients with CrCl <50 ml/min.

#### 5.4.5.C Overdose

No details are provided in the SPC; cases of overdose should therefore be discussed on a case-by-case basis with the TMG.

#### 5.4.5.D Stopping drug early

Discontinuation criteria for all regimens are considered in **Section 5.7.**

#### 5.4.5.E Missed doses

Patients should be instructed that if vomiting occurs **within** 5 hours of dosing an additional tablet of the trial drug should be taken. If vomiting occurs more than 5 hours after dosing, no further dose is needed.

If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. Patients should be instructed **not to** take a double dose. Any doses missed during the treatment course should be taken at the end of the prescribed course.

## 5.5 GLECAPREVIR/PIBRENTASVIR (MAVIRET®)

### 5.5.1 PRODUCT

The fixed dose combination of glecaprevir/pibrentasvir is a pangenotypic DAA regimen manufactured by Abbvie. Each film-coated tablet contains 100mg glecaprevir and 40mg pibrentasvir (total daily dosage of three tablets – 300mg glecaprevir and 120mg pibrentasvir – taken once a day). Patients should be instructed to swallow tablets whole with food and not to chew, crush or break the tablets as it may alter the bioavailability of the agents.

### 5.5.2 TREATMENT SCHEDULE

The duration of first-line glecaprevir/pibrentasvir treatment will be determined by the randomisation to varying versus fixed duration, as described in **Section 5.7** below.

### 5.5.3 DISPENSING

Glecaprevir/pibrentasvir will be dispensed by the pharmacist in the site pharmacy. There are no special storage requirements for the drug. Glecaprevir/pibrentasvir is packaged in aluminium foil blister packs; each pack contains 84 (4 x 21) film-coated tablets. For patients receiving 8 weeks first-line, drug will be dispensed every 4 weeks. For patients randomised to varying first-line duration, 4 weeks will be dispensed at the enrolment visit: at the week 4 visit, the precise number of days of treatment remaining will be dispensed by dividing packages before labelling.

### 5.5.4 DRUG-DRUG INTERACTIONS

Concomitant use with atazanavir-containing products, atorvastatin, simvastatin, dabigatran etexilate, ethinyl oestradiol-containing products, strong P-gp and CYP3A inducers (e.g., rifampicin, carbamazepine, St. John's wort (*Hypericum perforatum*), phenobarbital, phenytoin, and primidone) are all contra-indicated.

Glecaprevir and pibrentasvir are inhibitors of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3. Co-administration may increase plasma concentrations of medicinal products that are substrates of P-gp (e.g. dabigatran etexilate, digoxin), BCRP (e.g. rosuvastatin), or OATP1B1/3 (e.g. atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin).

Medicinal products that are strong P-gp and CYP3A inducers (e.g., rifampicin, carbamazepine, St. John's wort (*Hypericum perforatum*), phenobarbital, phenytoin, and primidone) could significantly decrease glecaprevir or pibrentasvir plasma concentrations and may lead to reduced therapeutic effect or loss of virologic response. Co-administration of such medicinal products is contraindicated. Co-administration with medicinal products that are moderate inducers P-gp/CYP3A may decrease glecaprevir and pibrentasvir plasma concentrations (e.g. oxcarbazepine, eslicarbazepine, lumacaftor, crizotinib). Co-administration of moderate inducers is not recommended. Co-administration with omeprazole 40 mg once daily may lead to reduced therapeutic effect and is not recommended.

Co-administration with atazanavir is contraindicated due to the risk of ALT elevations. Co-administration with efavirenz may lead to reduced therapeutic effect of Maviret and is not recommended. No clinically significant interactions are expected with tenofovir disoproxil fumarate. Co-administration with darunavir or lopinavir/ritonavir is not recommended.

In addition, the tablets contain the following excipients: Copovidone (type K 28), vitamin E (tocopherol) polyethylene glycol succinate, colloidal anhydrous silica, propylene glycol monocaprylate (type II), croscarmellose sodium, sodium stearyl fumarate, hypromellose 2910

(E464), lactose monohydrate, titanium dioxide, macrogol 3350, iron oxide red (E172). Hypersensitivity to any of these components is a contraindication to receipt.

### 5.5.5 DOSE MODIFICATIONS, INTERRUPTIONS & DISCONTINUATIONS

#### 5.5.5.A Hepatic impairment

No dose adjustment of Maviret is required in patients with mild hepatic impairment (Child-Pugh A). Maviret is not recommended in patients with moderate hepatic impairment (Child Pugh-B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C). As only patients with mild disease are eligible for the trial, no dose adjustment is necessary.

#### 5.5.5.B Renal impairment

No dose adjustment of Maviret is required in patients with any degree of renal impairment including patients on dialysis.

#### 5.5.5.C Overdose

The highest documented doses administered to healthy volunteers is 1,200 mg once daily for 7 days for glecaprevir and 600 mg once daily for 10 days for pibrentasvir. Asymptomatic serum ALT elevations (>5x ULN) were observed in 1 out of 70 healthy subjects following multiple doses of glecaprevir (700 mg or 800 mg) once daily for ≥ 7 days. In case of overdose, the patient should be monitored for any signs and symptoms of toxicities. Appropriate symptomatic treatment should be instituted immediately. Glecaprevir and pibrentasvir are not significantly removed by haemodialysis. All cases of suspected overdose should be discussed with the TMG.

#### 5.5.5.D Stopping drug early

Discontinuation criteria for all regimens are considered in **Section 5.7.**

#### 5.5.5.E Missed doses

Patients should be instructed that if vomiting occurs **within** 3 hours of dosing an additional tablet of the trial drug should be taken. If vomiting occurs more than 3 hours after dosing, no further dose is needed.

If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. Patients should be instructed **not to** take a double dose. Any doses missed during the treatment course should be taken at the end of the prescribed course.

## 5.6 RIBAVIRIN

### 5.6.1 PRODUCTS

Ribavirin film-coated tablets (or hard capsules) contain either 200mg or 400mg of ribavirin per tablet. The standard dose is weight-based (see **Table 9** below). Ribavirin is administered orally each day in two divided doses (morning and evening) with food. The tablets/capsules should not be chewed or crushed.

**Table 9 Weight-based ribavirin dosing**

| Medicinal product used in combination | Weight based daily ribavirin dose | Number of 200mg ribavirin tablets |
|---|---|---|

| | | |
|---|---|---|
| DAA | body weight <75kg: 1000mg | 5 x 200mg (2 morning, 3 evening) |
| | body weight ≥75kg: 1200mg | 6 x 200mg (3 morning, 3 evening) |

### 5.6.2 TREATMENT SCHEDULE

Ribavirin will be given for an identical duration to first-line DAAs, following the randomisation to varying versus fixed duration, as described in **Section 5.7** below.

Ribavirin re-treatment, following confirmed virological failure on first-line, will be 12 weeks.

### 5.6.3 DISPENSING

Ribavirin will be dispensed by the pharmacist in the site pharmacy. There are no special storage requirements for the drug. The drug is teratogenic and the capsules/film coated tablets must not be broken or crushed. The commercial drug comes in bottles containing 28, 42, 112 or 168 tablets. For patients receiving 8 weeks first-line or 12 weeks re-treatment, ribavirin will be dispensed every 4 weeks. For patients randomised to varying first-line duration, 4 weeks will be dispensed at the enrolment visit: at the week 4 visit, the precise number of days of treatment remaining will be dispensed. If a patient previously weighing >75 kg has lost weight and falls to more than 2.5kg below the 75 kg body-weight threshold at the day 28 visit on first-line or at the re-treatment week 4 or week 8 visits, then ribavirin dose adjustment should be undertaken as above. Similarly if a patient previously weighing <75 kg has gained weight and increases to more than 2.5kg above the 75 kg body-weight threshold at the week 4 visit, ribavirin dose adjustment should be undertaken as above. The 2.5kg window is designed to avoid repeatedly changing doses in patients whose weight is fluctuating around the fixed 75kg threshold.

### 5.6.4 DRUG-DRUG INTERACTIONS

The half-life of ribavirin is very long, and the activity of the drug may persist for approximately 2 months after cessation. This long activity has to be considered in terms of potential for drug-drug interactions, specifically

- Ribavirin increases the levels of the azathioprine metabolite, 6-methylthioinosine monophosphate, with the potential for increased myelotoxicity. The combination should be avoided if at all possible.
- Ribavirin also inhibits phosphorylation of several HIV reverse transcriptase inhibitor zidovudine (ZDV), and stavudine. While stavudine is now a completely obsolete in the UK, ZDV is still used. Patients on ZDV-based regimens should be switched away from the drug to a suitable alternative before, during and for at least 2 months post ribavirin exposure on study to avoid the theoretical risk of loss of HIV viral control;
- Didanosine is a virtually obsolete anti-HIV drug in the UK; it is absolutely contraindicated with ribavirin. Ribavirin increases levels of didanosine and fatal hepatotoxicity, lactic acidosis, and pancreatitis have been reported during co-administration.

See also www.hep-druginteractions.org.

In addition, ribavirin contains the following excipients:
1) Rebetol®: Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Magnesium stearate, Gelatine, Titanium dioxide, Shellac, Propylene glycol, Ammonium hydroxide, Colouring agent (E 132);
2) Copegus®: Pregelatinised maize starch, Sodium starch glycolate (type A), Microcrystalline cellulose, Maize starch, Magnesium stearate, Hypromellose, Talc, Titanium dioxide (E171), Yellow iron oxide (E172), Red iron oxide (E172), Ethylcellulose aqueous dispersion, Triacetin;

3) ribavirin generic (Aurobindo Pharma - Milpharm Ltd): Cellulose, microcrystalline, Starch, pregelatinised (Maize starch), Sodium starch glycolate (Type A), Povidone (K-30), Silica, colloidal anhydrous, Magnesium stearate, HPMC 2910/ Hypromellose (15cP) (E464), Titanium dioxide (E171), Triacetin (E1518), Iron oxide red (E172), Iron oxide yellow (E172), Ethyl cellulose (10cP) (E462)
4) ribavirin generic (TEVA): Calcium hydrogen phosphate, Croscarmellose sodium, Povidone, Magnesium stearate, Titanium dioxide (E171) Gelatin, Shellac, Titanium dioxide (E171), Indigo carmine
5) ribavirin Mylan: Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Povidone, Gelatin, Titanium dioxide (E171), Shellac, Propylene glycol, Ammonia solution, concentrated, Yellow iron oxide (E172), Indigotine (E132),Titanium dioxide (E171).
Hypersensitivity to any of these components is a contraindication to receipt.

### 5.6.5 Dose Modifications, Interruptions & Discontinuations

#### 5.6.5.A Anaemia

**Table 10** below provides guidelines for dose modifications and discontinuation based on the patient's haemoglobin concentration and cardiac status. These should be applied for ribavirin used as either first-line treatment or re-treatment.

**Table 10 Ribavirin dose modification for anaemia**

| Laboratory values | Reduce ribavirin dose to 600 mg/day if: | Discontinue ribavirin if: |
|---|---|---|
| Haemoglobin in patients with no cardiac disease | < 10 g/dL | < 8.5 g/dL |
| Haemoglobin in patients with history of stable cardiac disease | ≥ 2 g/dL decrease in haemoglobin during any 4-week treatment period | < 12 g/dL despite 4 weeks at reduced dose |

Once ribavirin has been withheld due to either a laboratory abnormality or clinical manifestation, an attempt may be made to restart ribavirin at 600 mg daily and further increase the dose to 800 mg daily. However, it is not recommended that ribavirin be increased to the originally assigned dose (1,000 mg to 1,200 mg daily). Intensive monitoring of haemoglobin concentrations, with corrective action as may be necessary, should be employed throughout the treatment period.

#### 5.6.5.B Renal impairment

Based on PK modelling and simulation, dose reductions are recommended in patients with significant renal impairment i.e. creatinine clearance (CrCl) <50 ml/min (**Table 11**). Whilst patients with CrCl <60ml/min are not eligible, other patients may develop renal impairment during the trial, in which case doses should be adjusted as below. These adjusted doses are expected to provide ribavirin plasma exposures comparable to those achieved in patients with normal renal function receiving the standard dose. Most of the recommended doses were derived from PK modelling and simulation and have not been studied in clinical trials.

**Table 11 Ribavirin dose modification for renal impairment**

| Creatinine Clearance (CrCl) | Ribavirin dose (daily) |
|---|---|
| 30 to 50 ml/min | Alternating doses, 200 mg and 400 mg every other day |
| < 30 ml/min | 200 mg daily |
| Hemodialysis | 200 mg daily |

CrCl <60 ml/min is an exclusion criteria for enrolment; however it is possible that those needing re-treatment could have developed renal impairment and this should be checked before commencing re-treatment. Ribavirin should be initiated, or continued if renal impairment develops while on therapy, with extreme caution in those with CrCl <50 ml/min.

#### 5.6.5.C Overdose

No cases of overdose of ribavirin have been reported in clinical trials. Hypocalcaemia and hypomagnesaemia have been observed in persons administered dosages greater than four times the maximal recommended dosages. In many of these instances ribavirin was administered intravenously. Due to the large volume of distribution of ribavirin, significant amounts of ribavirin are not effectively removed by haemodialysis.

#### 5.6.5.D Stopping drug early

Discontinuation criteria are considered in **Section 5.7.**

#### 5.6.5.E Missed doses

Patients should be instructed that if vomiting occurs **within 6** hours of dosing an additional dose of trial drug should be taken. If vomiting occurs more than 6 hours after dosing, no further dose is needed.

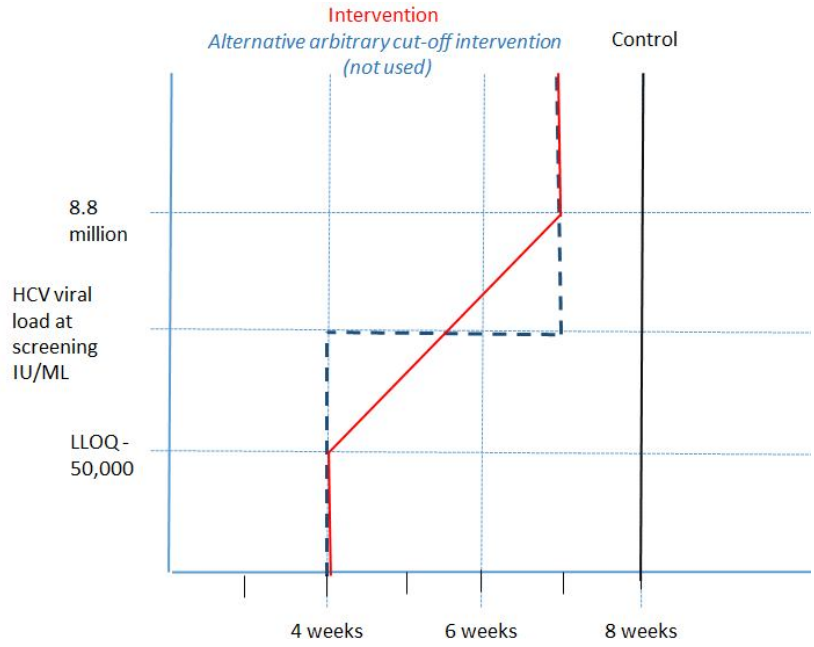
If a dose is missed, the prescribed dose can be taken within 6 hours. If more than 6 hours have passed since the drug is usually taken, the missed dose should NOT be taken and the patient should take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose. Any doses missed during the treatment course should be taken at the end of the prescribed course.

## 5.7 DURATION OF FIRST-LINE TREATMENT

### 5.7.1 TREATMENT SCHEDULE

In comparison to the fixed (control) 8 weeks first-line treatment, the intervention duration will be between 4-7 weeks first-line treatment, on a sliding scale determined by the screening HCV viral load (see solid red line on **Figure 2**). The proposed stratification rule is determined from the mean and standard deviation baseline viral load, and the mean estimated declines, from previous trials (mean screening VL ~6.25 $\log_{10}$ IU/ml, SD 0.4; mean estimated decline 2.15 $\log_{10}$ IU/ml per week). Together these can be used to estimate the duration of treatment needed to reduce levels to ~1 copy in the whole body at end of treatment (<0.0001 IU/ml), including a conservative assumption of a moderate negative correlation between baseline and decline in viral load since no data are available on this parameter. An alternative "cut-point" rule (shown in dashed blue line on **Figure 2**) would require a single threshold HCV VL to be chosen, and reflects biological variation less well.

**Figure 2 Biomarker stratified varying first-line treatment duration**




This biomarker-stratified treatment duration will be implemented as a specific number of days of first-line treatment based on the screening VL, as shown in **Table** 12 below. (Note that the declines are linear on a log scale, so that the absolute IU/ml do not increase linearly across the categories.) Based on recent trials, we would expect ~15% of recruited patients (with screening HCV VL <10,000,000IU/ml) to receive 4 weeks treatment and ~5% to receive 7 weeks treatment.

**Table 12 Duration of first-line treatment in the intervention biomarker-stratified group**

| From HCV VL (IU/ml) | To HCV VL (IU/ml) | Days |
|---|---|---|
| LLOQ | 50,000 | 28 |
| 50,001 | 65,000 | 29 |
| 65,001 | 82,500 | 30 |
| 82,501 | 110,000 | 31 |
| 110,001 | 140,000 | 32 |
| 140,001 | 180,000 | 33 |
| 180,001 | 235,000 | 34 |
| 235,001 | 300,000 | 35 |
| 300,001 | 400,000 | 36 |
| 400,001 | 500,000 | 37 |
| 500,001 | 650,000 | 38 |
| 650,001 | 850,000 | 39 |
| 850,001 | 1,100,000 | 40 |
| 1,100,001 | 1,450,000 | 41 |
| 1,450,001 | 1,850,000 | 42 |
| 1,850,001 | 2,400,000 | 43 |
| 2,400,001 | 3,150,000 | 44 |
| 3,150,001 | 4,100,000 | 45 |
| 4,100,001 | 5,250,000 | 46 |
| 5,250,001 | 6,800,000 | 47 |
| 6,800,001 | 8,800,000 | 48 |
| 8,800,001 | upwards | 49 |

All patients will be prescribed the first 4 weeks of first-line therapy at randomisation; the remainder of their first-line treatment (as per their randomised group) will be provided at the week 4 visit. If a patient previously weighing >75 kg has lost weight and falls below the 75 kg body-weight threshold at the week 4 visit, ribavirin dose adjustment should be undertaken as per the guidance in **Section 5.6.1**.

All patients will be offered an optional patient diary card personalised with their specific combination regimen (tablets and OD/BD) and treatment duration to help them record pill taking. Any doses missed during the treatment course should be taken at the end of the prescribed course.

### 5.7.2 CHOICE OF 8 WEEK FIRST-LINE FIXED DURATION CONTROL GROUP

Both the ombitasvir/paritaprevir/(dasabuvir)/ritonavir and the sofosbuvir/ledipasvir combinations are licenced as 12 week treatments for the cure of Hepatitis C. However, several trials comparing fixed shorter durations are ongoing or have promising results (see **Section 1.3**), such that the vast majority of patients are still likely to achieve cure with 8 weeks treatment. Glecaprevir/pibrentasvir is licensed as an 8 week treatment without ribavirin. Within this protocol therefore, the duration of first-line treatment will be fixed at 8 weeks. All patients who do not achieve cure with 8 weeks treatment will receive re-treatment with 12 weeks' sofosbuvir/ledipasvir/ribavirin within the protocol, such that their overall probability of being cured within the trial is estimated to be 98% (see **Section 9.3**). The primary endpoint of the trial is the overall cure rate after first-line and re-treatment, specifically to address the question as to whether failing on a shorter duration treatment ultimately affects overall chance of cure, or whether the percentages cured with shorter treatment can make it more cost-effective to give everyone shorter courses initially, and then retreat those who do not achieve cure. The specific first-line cure rates are not critical to answering either of these questions.

## 5.8 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, patients are consenting to trial treatment, trial follow-up and data collection.

Randomised treatment (or re-treatment) will be discontinued if any of the following occur:

- toxicity which the investigator considers impedes the ability of the patient to continue the trial drug and/or the product information for the drug(s) contains a directive on discontinuation in the event of this specific toxicity (see **Sections 5.3.5, 5.4.5, 5.5.5 and 5.6.5** above)
- a female participant currently receiving trial drugs, or the female partner of a male participant currently receiving trial drugs, becomes pregnant
- patient request for any reason to withdraw consent for treatment
- virological failure as defined in **Section 5.2** above (move to re-treatment if first-line failure)
- any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion
- the study is discontinued at the request of funder, sponsor or ethics committee.

Except for the last scenario, patients discontinuing treatment will continue scheduled follow-up visits "off study drug, on study" and should not be considered as automatically withdrawn from the study as a whole. In particular, any patient ceasing randomised first-line treatment for any reason and subsequently meeting failure criteria above would move to the re-treatment phase (although

obviously patients have the right to refuse re-treatment; any such patient would remain "off study drug, on study").

As the patient's participation in the trial is entirely voluntary, they may choose to discontinue the trial treatment at any time without penalty. Although the patient is not required to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason while fully respecting the patient's rights.

Patients should remain in the trial for the purpose of follow-up and data analysis "off study drug, on study" (unless the patient withdraws their consent from all stages of the trial). Only if a patient no longer wishes to continue attending follow-up visits will they cease follow-up and be considered "off study": in this scenario, patients would be asked whether they would be happy for their routine electronic data to be used in the study to determine outcomes. If a patient is withdrawn from follow-up, refer to **Section 6.6**.

Data will be kept and included for patients who stop follow-up early.

## 5.9 ACCOUNTABILITY & UNUSED DRUGS

Investigational Medicinal Product (IMP) will be obtained by the NHS pharmacy at each of the participating sites following standard commissioning. The hospital pharmacy will document receipt of supplies and returns using their standard procedures.

IMP accountability will be maintained and monitored by site staff and MRC CTU at UCL respectively according to the STOPHCV-1 working practices. Unused drug must be returned to the clinic (and will be counted). The clinic will then return the drug to the site pharmacy. All drug dispensed at and returned to the site pharmacy should be documented on a site Accountability Log, maintained by a named person (trial pharmacist or research nurse). The designated trial pharmacist/nurse will, on receipt of supplies prior to the commencement of the trial, conduct an inventory and complete a receipt. It is recommended that inventories be conducted monthly. Procedures for labelling, accountability, and destruction will be detailed in the STOP-HCV-1 working practice documents. MRC CTU at UCL will monitor drug accountability at site visits. At the end of the trial all unlabelled, unused, non-expired drug will be checked against the inventory before being returned to source, and pill returns or bottles that have been dispensed and returned by participants will be checked against the inventory before disposal on site according to local pharmacy guidelines and applicable regulations. Documentation of disposal will be provided to MRC CTU at UCL.

## 5.10 COMPLIANCE & ADHERENCE

As the intervention will start immediately following randomisation, suitable patient information and fully informed consent procedures will ensure that patients understand the trial requirements. Therefore, any non-compliance will likely be a consequence of the intervention itself (e.g. drug intolerance or toxicity) which would also likely occur if it were incorporated within clinical practice, i.e. non-compliance will likely be part of the pragmatic strategy being evaluated and an intention-to-treat comparison will therefore incorporate the level of non-compliance as would be anticipated in general clinical practice.

Drop-out from clinical trials conducted to gain approval for DAAs has been low (<5%). The reasons for this are (i) that the oral treatments are much better tolerated than existing (interferon, injectable) therapy (ii) the treatments offer high likelihood of cure and thus patients are likely to be

motivated to complete therapy (iii) for most patients in the study, treatment duration will be much shorter than conventional therapy and thus adherence is likely to be high. Compliance and adherence to the prescribed treatment regimen will be assessed at clinic visits. Patients will be asked to return with their prescribed medication for pill counts, and will also be asked about self-reported adherence.

## 5.11 TREATMENT DATA COLLECTION

Every DAA prescribed (and ribavirin), its dose, frequency, and duration will be recorded in the CRF.

## 5.12 NON-TRIAL TREATMENT

The choice and duration of other medications to accompany the IMP will be left to the discretion of the treating physician. These medications will be recorded on CRFs. All medications are permitted other than those listed as not permitted in **Sections 5.3.4, 5.4.4, 5.5.5 and 5.6.4**.

### 5.12.1 ANTIRETROVIRAL DRUGS IN HIV-HCV CO-INFECTED PATIENTS RECEIVING OMBITASVIR/PARITAPREVIR/(DASABUVIR)/RITONAVIR OR GLECAPREVIR/PIBRENTASVIR

Ombitasvir/paritaprevir/(dasabuvir)/ritonavir contains ritonavir which is used as a pharmacokinetic enhancer to boost the blood levels of several protease inhibitors used to treat HIV infection. Atazanavir is contraindicated and darunavir is not recommended with glecaprevir/pibrentasivir. Antiretroviral medications must therefore be reviewed in any HIV co-infected patient being treated with either combination.

The SPC for the trial IMP details which antiretroviral therapy (ART) can be safely administered. **Table 13** below summarises which ART **can** be administered in HIV-HCV co-infected patients receiving ombitasvir/paritaprevir/(dasabuvir)/ritonavir or glecaprevir/pibrentasvir during STOP-HCV-1 participation. However, because patients should not be changed mid trial from one ART combination to the other, we recommend the following ART regimens for patients receiving ombitasvir/paritaprevir/(dasabuvir)/ritonavir:
1) Truvada® with standard dose raltegravir or dolutegravir or
2) Truvada® with standard dose darunavir (800mg QD) or atazanavir (300mg QD) without ritonavir or cobicistat when receiving ombitasvir/paritaprevir/(dasabuvir)/ritonavir and with additional ritonavir (100mg QD) or cobicistat, as boosting agents, when not on ombitasvir/paritaprevir/(dasabuvir)/ritonavir.

The protease inhibitors atazanavir (contraindicated), darunavir (not recommended) and lopinavir (not recommended) should not be used in patients receiving the glecaprevir/pibrentasvir regimen. Therefore, we recommend the following ART regimens for such patients:
1) Truvada® with standard dose raltegravir or dolutegravir

**Table 13 Antiretrovirals which can be administered during STOP-HCV-1**

| **STOP-HCV-1 IMP** | Nucleoside reverse transcriptase inhibitor (NRTI) | Protease inhibitor (PI) | Integrase inhibitor (INSTI) | Nucleoside reverse transcriptase inhibitor (NNRTI) |
|---|---|---|---|---|
| Ribavirin | Truvada® or TDF/3TC<br><br>Kivexa® or ABC/3TC | see restrictions under the specific DAA sections | see restrictions under the specific DAA sections | see restrictions under the specific DAA sections |
| | | | | |
| Ombitasvir/paritaprevir/ (dasabuvir)/ritonavir | Truvada® or TDF/3TC<br><br>Kivexa® or ABC/3TC | atazanavir* 300mg (**no additional ritonavir or cobicistat**)<br>darunavir 800mg (**no additional ritonavir or cobicistat**) | raltegravir 400mg BID (standard dose)<br><br>dolutegravir 50mg QD (standard dose) | rilpivirine 25mg QD (standard dose) **ONLY** if no actual or risk of QTc prolongation |
| | | | | |
| Sofosbuvir/ledipasvir | Truvada® or TDF/3TC<br><br>Kivexa® or ABC/3TC | atazanavir*/r (300/100mg)<br>darunavir/r (800mg/100mg) | raltegravir 400mg BID (standard dose)<br><br>dolutegravir 50mg QD (standard dose) | rilpivirine 25mg QD |
| | | | | |
| Glecaprevir/pibrentasvir | Truvada® or TDF/3TC<br><br>Kivexa® or ABC/3TC | | raltegravir 400mg BID (standard dose)<br><br>dolutegravir 50mg QD (standard dose) | rilpivirine 25mg QD |
| * increased risk of hyperbilirubinaemia especially if ribavirin is co-administered | | | | |

### 5.12.2 TREATMENT AFTER TRIAL EVENT

The trial protocol specifies treatment regimens for first-line and re-treatment phases. Any subsequent treatment in the case of overall failure will be at the discretion of the responsible physician according to the availability of novel agents through NHS commissioning.

# 6 ASSESSMENTS & FOLLOW-UP

All patients will be followed by the site clinic teams for 24 weeks after the end of first-line treatment or re-treatment (where relevant) for evaluation of virological response and toxicity. Subsequent long-term follow-up will be electronic through hospital and national records (consent will be sought for this as part of the consent for trial participation). Outcome measures will be assessed at clinic visits (see **Table 1** p10). The on treatment visits should occur within ±1 days wherever possible, and the post end-of-treatment (EOT) visits in hospital within ±3 days. However, if this is not possible, a visit (with all the appropriate tests and evaluations) should still take place outside this window to ensure that trial outcomes are ascertained as accurately as possible in real-time. In particular the Day 3 visit must occur 3 or more calendar days before the Day 7 visit (that is, there should be two calendar days completely separating them).

All those recording clinical data will be identified by each site PI, receive appropriate training and sign the Delegation Log. Clinical data will be obtained through consultation with the patient, their medical team, or their medical records. Laboratory measures and resource utilisation will be extracted from patient notes/electronic records; study nurses will administer quality of life questionnaires to patients.

Any additional visits or diagnostic/laboratory tests needed for patient management should occur as required at the discretion of the treating physician. Results from these investigations should be recorded on STOP-HCV-1 CRFs, but only the investigations specified in **Table 1** (p10) are required in all patients.

## 6.1 TRIAL ASSESSMENT SCHEDULE

Randomisation may occur on any day of the week, but this places restrictions on the timing of the Day 3 visit required in all patients to enable early kinetics of HCV RNA response to be determined (see **Table 8**).

Visits will be on day 3, 7, 14 and 28 after randomisation: then end of (first-line) treatment (EOT); then 4-weekly until 12 weeks post EOT, then 24 weeks post EOT. Visits are counted from EOT following standard practice in HCV trials. See **Table 1** (p10). The Day 3 visit must occur 3 or more calendar days before the Day 7 visit (that is, there should be two calendar days completely separating them).

Patients who fail first-line will move to the 12 weeks of the alternative DAA regimen with ribavirin for 12 weeks; visits will be week 2, 4, 8, 12 (EOT) of re-treatment; then 4, 8, 12 and 24 weeks after EOT. See **Table 3** (p13).

Every visit will include a clinical assessment for adverse event outcomes and blood draw for HCV viral load, plus standard scheduled safety tests at specified visits.

## 6.2 PROCEDURES FOR ASSESSING EFFICACY

HCV viral load will be assayed locally; all participating centres currently provide these assays for clinical practice and participate in quality assurance schemes. This will also enable swift detection of virological failure and move to re-treatment.

HCV viral resistance will be measured within the STOP-HCV consortium retrospectively in batches during the trial. This will be done using next-generation sequencing approaches. Viral genotype will also be characterised using these assays enabling an assessment of whether treatment failure is a genuine recurrence (same genotype, closely genetically related) or a new infection (different genotype, or same genotype but genetically too distant to be compatible with within-host evolution). In terms of incidental findings from these next generation sequencing studies, we will follow the STOP-HCV Consortium's Policy on Health Related Findings (HRFs), specifically that

- HRFs identified during viral genetics studies that are associated with serious and treatable infectious disease WILL be fed back to patients. The STOP-HCV HRF working group agreed that the only pathogens falling within this category of HRFs at the current time were HIV and Hepatitis B.
- HRFs identified during host genetics studies will NOT be fed back to patients.

## 6.3 PROCEDURES FOR ASSESSING SAFETY

Safety laboratory assessments will be performed, and clinical AEs and SAEs solicited (together with relationship to study medications), throughout the study at clinical visits.

Laboratory abnormalities (in particular, clinical chemistry and haematology) that require medical or surgical intervention or lead to an interruption, modification, or discontinuation in study medication will be recorded as an AE, as well as an SAE (if applicable). In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE (see **Section 7.1**, p62). The severity grading of AEs will be assessed as Grade 1, 2, 3, or 4 using the Division of AIDS table for grading the severity of adult and paediatric adverse events and reported on CRFs. If the laboratory abnormality is part of a syndrome, the diagnosis or syndrome will be recorded (eg, anaemia), in preference to the laboratory result. All adverse events will be coded from the verbatim text using MedDRA.

All AEs should be recorded in the patient's notes: only those which are

- grade 3 or 4 adverse events or reactions,
- serious (SAEs), or
- lead to modification of one or more trial drugs (any grade)

need to be reported on trial CRFs.

See **Safety Reporting Section 7** and **Section 7.3** (p64) in particular for investigator's responsibilities regarding assessment of seriousness, causality and expectedness, and reporting to the MRC Clinical Trials Unit (CTU).

Any patient experiencing an AE or SAE will be followed up until resolution of the AE. For AE/SAE leading to discontinuation of study medication, patients will continue to be followed up "off study drug, on study". Any patient who wishes to withdraw from study visits after an AE/SAE leading to discontinuation of study medication must still be followed up in routine clinics for 12 weeks following cessation of therapy.

## 6.4 OTHER ASSESSMENTS

Patients will be asked to complete the EuroQol-5D questionnaire (EQ-5D) at day 0/week 0, EOT and 12 weeks post-EOT for both first-line and any re-treatment. These assessments will be used to

inform the cost effectiveness of the different strategies. At the same timepoints, patients will also complete the Medical Outcomes Study Short-Form 12 Item Survey (SF-12, version 2)[1] and the Cognitive Function Scale[2] (MOSCOG). The SF-12 is a generic measure of health related quality of life; and the self-rating of cognitive symptoms from the 6 questions on MOSCOG correlates well with formal cognitive testing in Hepatitis-C infected patients (personal communication, Daniel Forton, unpublished). For the SF-12, there are 8 domains and two summary scores, the Physical Health Component Summary (PCS) and the Mental Health Component Summary (MCS).

The trial will measure the healthcare-related costs of patients in the trial from enrolment to last follow-up. Information on resource utilisation (including non-trial procedures, laboratory tests and concomitant medications) will be collected at the regular clinical assessments. Within trial assessments of health related quality of life (using the EQ5D) will also be used in the economic analysis. EQ5D scores will be used to weight lifetime lived by its quality; the EQ5D tariff developed for the UK will be used to derive the scores from the patient's responses to the EQ5D descriptive system[41]. The cost effectiveness analysis will thus use QALY (Quality Adjusted Life Years) as the outcome measure (further details in **Section 9.6**).

Self-reported adherence will be assessed using questions about the numbers of each drug that the patients should be taking (knowledge), the numbers of days in the last week when the patient did not take all their doses or any doses (separately), whether the patient has missed doses for 2 or more consecutive days in the last month, or at weekends, and reasons for missing doses.

## 6.5 EARLY STOPPING OF FOLLOW-UP

If a patient chooses to discontinue their trial treatment, they should always be followed up "off study drug, on study" providing they are willing, that is, they should be encouraged to not leave the whole trial. If they do not wish to remain on trial follow-up, however, their decision must be respected and the patient will be withdrawn from the trial. However, in this situation, the patient should be asked whether or not they are willing to provide follow-up through routine electronic records (that is, not to attend study-specific visits but to allow data collected within the NHS to be used for trial comparisons). The MRC CTU at UCL should be informed of the patient's decision regarding withdrawal (no further data of any kind, or follow-up through electronic medical records) in writing using the appropriate CRF. Prior to withdrawing from the trial, the patient will be asked to have assessments performed as appropriate for the final EOT+24 week visit although they would be at liberty to refuse any or all individual components of the assessment.

If a patient withdraws from the trial, the medical data collected during their previous consented participation in the trial will be kept and used in analysis. Consent for future use of stored samples already collected can be refused when leaving the trial early (but this should be discouraged and should follow a discussion). If consent for future use of stored samples already collected is refused, then all such samples will be destroyed following the policies of the institution where the samples reside at the time (local or central storage).

Patients may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial, including taking repeat samples.

Patients who stop trial follow-up early will not be replaced, as the total sample size includes adjustment for losses to follow-up.

Consent will be sought for long-term follow-up through electronic NHS records in order to ascertain long-term impact of treatment on morbidity and mortality including cirrhosis and hepatocellular

carcinoma. This will require collection of NHS numbers, which will be stored in a separate database from the main trial data linked only to the patient's trial number.

## 6.6 PATIENT TRANSFERS

If a patient moves from the area, every effort should be made for the patient to be seen at another participating trial site. A copy of the patient's CRFs should be provided to the new site and the patient will need to sign a new consent form. Once this has been done, the new site will take over responsibility for the patient; until this has been done, responsibility for the patient and any outstanding queries (up to the point of transfer) lies with the original site.

## 6.7 LOSS TO FOLLOW-UP

In the statistical analysis, a patient will be classified as 'lost to follow-up' if they have not been seen at the final EOT+24 week visit within a [-6,+6] week window.

## 6.8 COMPLETION OF PROTOCOL FOLLOW UP

The trial will end after the final first-line or re-treatment EOT+24 week visit of all randomised patients. Because the trial contains a re-treatment phase, this may not necessarily be the final EOT+24 week visit of the last randomised patient.

However, we expect that Hepatitis C infection may lead to longer term complications even after cure, including liver cancers, which may take a long time to manifest. For this reason, we will ask for permission to check patient's medical records to provide long-term electronic follow-up for the rest of their life for outcomes relating to Hepatitis C infection. This follows the approach taken by Genome England for long-term electronic follow-up.

# 7 SAFETY REPORTING

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. **Section 7.1** lists definitions, **Section 7.3** gives details of the investigator responsibilities and **Section 7.4** provides information on MRC CTU at UCL responsibilities.

## 7.1 DEFINITIONS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of GCP apply to this trial protocol. These definitions are given in **Table 14**.

**Table 14 Definitions**

| TERM | DEFINITION |
|---|---|
| Adverse Event (AE) | Any untoward medical occurrence in a patient or clinical trial participant to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | Any untoward and unintended response to an investigational medicinal product related to any dose administered. |
| Unexpected Adverse Reaction (UAR) | An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product. |
| Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR) | Respectively any adverse event, adverse reaction or unexpected adverse reaction that:<br>▪ Results in death<br>▪ Is life-threatening*<br>▪ Requires hospitalisation or prolongation of existing hospitalisation**<br>▪ Results in persistent or significant disability or incapacity<br>▪ Consists of a congenital anomaly or birth defect<br>▪ Is another important medical condition*** |

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

### 7.1.1 MEDICINAL PRODUCTS

An investigational medicinal product is defined as the tested investigational medicinal product (IMP) and the comparators used in the study (EU guidance ENTR/CT 3, April 2006 revision).

In this protocol, IMP is therefore

- ombitasvir/paritaprevir/ritonavir
- dasabuvir
- sofosbuvir/ledipasvir
- glecaprevir/pibrentasvir
- ribavirin

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP or comparator should be reported appropriately.

### 7.1.2 ADVERSE EVENTS

Adverse Events include:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

### 7.1.3 EXEMPTED ADVERSE EVENTS

Adverse Events do not include:

- Medical or surgical procedures; the condition that leads to the procedure is the adverse event
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, eg, elective cosmetic surgery, social admissions
- Overdose of medication without signs or symptoms

### 7.1.4 DISEASE-RELATED EVENTS

All HCV-related events which meet the definitions above should be reported as adverse events.

### 7.1.5 OTHER STUDY-SPECIFIC REQUIREMENTS

All AEs should be recorded in the patients notes: only those which are grade 3 or 4 adverse events or reactions, serious (SAEs) or lead to modification of one or more trial drugs (any grade) need to be reported on trial CRFs.

## 7.2 OTHER NOTABLE EVENTS

### 7.2.1 PREGNANCY

The oral DAAs are pregnancy category B drugs. Ribavirin is a Category X drug in pregnancy. As all patients will be randomised to receive or not receive adjunctive ribavirin, being pregnant or intending to become pregnant (self or partner) is an exclusion criteria. Hence, women of child-bearing potential must avoid pregnancy for the duration of the study and for ≥4 months after ribavirin exposure[39] _ENREF_33. Male patients must avoid pregnancy in their female partners for ≥7

months after ribavirin exposure because of the prolonged negative impact on normal spermatogenesis seen in animal models. Those not randomised to ribavirin should also avoid pregnancy, given the potential to take ribavirin as part of re-treatment and, given the short duration of treatment, as relatively little is known about the oral DAAs in pregnancy.

Pregnancies that during the trial, either in a patient or in a female partner of a male patient (with their specific consent) will be reported as an SAE during the active phase of follow-up. All female patients will be followed for at least 4 months (16 weeks) as part of the trial follow-up schedule (to 24 weeks post EOT). Pregnancies in the female partners of male patients will be ascertained at this EOT+24 week visit and at the patients next routine clinic visit outside the trial (to cover the 7 month cut-off for ribavirin exposure in male patients). Information on pregnancy outcome will be reported to the MHRA. Although it is unknown to what extent ribavirin is excreted in breast milk, the SPC recommends avoiding breast-feeding during ribavirin receipt.

## 7.3 INVESTIGATOR RESPONSIBILITIES

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes; those which are:

- grade 3 or 4 adverse events or reactions
- lead to modification (temporary or permanent interruption or change in dose, any grade)

should be reported in the toxicity (symptoms) section of the Follow-up CRF and sent to the MRC CTU at UCL within 31 days.

SAEs and SARs should be notified to the MRC CTU at UCL within 24 hours of the investigator becoming aware of the event.

### 7.3.1 INVESTIGATOR ASSESSMENT

#### 7.3.1.A Seriousness

When an AE or AR occurs, the investigator responsible for the care of the patient must first assess whether or not the event is serious using the definition given in **Table 14**. If the event is serious, then an SAE Form must be completed and the MRC CTU at UCL notified within 24 hours.

#### 7.3.1.B Severity or grading of adverse events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity gradings in the Division of AIDS table for grading the severity of adult and paediatric adverse events

(http://rsc.tech-res.com/document/safetyandpharmacovigilance/table_for_grading_severity_of_adult_pediatric_adverse_events.pdf).

#### 7.3.1.C Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in

**Table** 15. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

**Table 15 Assigning Type of SAE Through Causality**

| RELATIONSHIP | DESCRIPTION | SAE TYPE |
|---|---|---|
| Unrelated | There is no evidence of any causal relationship | Unrelated SAE |
| Unlikely | There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the patient's clinical condition, other concomitant treatment). | Unrelated SAE |
| Possible | There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the patient's clinical condition, other concomitant treatments). | SAR |
| Probable | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. | SAR |
| Definitely | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. | SAR |

If an SAE is considered to be related to trial treatment and drug is stopped or the dose modified, refer to **Sections 5.3.5, 5.4.5 and 5.6.5**.

### 7.3.1.D Expectedness

If there is at least a possible involvement of a trial treatment, the investigator should make an initial assessment of the expectedness of the event, however the Sponsor has the final responsibility for determination of expectedness. An unexpected adverse reaction is one not previously reported in the current Summary of Product Characteristics (SPC) or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in **Table 14**. If a SAR is assessed as being unexpected, it becomes a SUSAR.

See **Table 16**, **Table 17, Table 18** and **Table 19** below for expected toxicities associated with the drugs being used in this trial[9,10,16,39]. Most of these side-effects were mild in severity.

Other side-effects associated with ombitasvir/paritaprevir/(dasabuvir)/ritonavir are

- **Abnormal liver function tests**: Around 1% of participants in trials in **Table 17** experienced quite high levels of ALT in the first few weeks after starting ombitasvir/paritaprevir/dasabuvir/ritonavir. This was much more commonly seen in women than men, and especially if the women were on a particular type of contraceptive pill (exclusion criteria).
- **Serum bilirubin elevations**: Transient elevations in serum bilirubin in around one-third of patients usually reached their peak by the first week of treatment, and resolved without any change in the treatment. The risk of bilirubin elevations was greater in those also on ribavirin.

- **HIV/HCV co-infection**: The overall safety profile was similar in HIV co- and mono-infection. Transient increases in total bilirubin mostly occurred in patients on atazanavir, which also increases bilirubin levels. Changes resolved without treatment modification.

**HCV/HBV co-infection**

- Cases of hepatitis B virus reactivation have been reported during or after treatment with **all** DAA agents, including those used in this protocol. Hepatitis B screening should be performed in all patients before initiation of DAA treatment. HBV/HCV co-infected patients are at a risk of HBV reactivation and should be monitored and managed according to clinical guidelines.

**Depression**

- Cases of depression and more rarely of suicidal ideation and suicide attempt have been reported with ombitasvir/paritaprevir/(dasbuvir) ritonavir treatment in combination with ribavirin in the majority of the cases. While psychiatric problems including depression are well described with ribavirin (**Table 19**) and although some patients had a previous history of depression, psychiatric illness and/or substance abuse, a causal relation with ombitasvir/paritaprevir/(dasbuvir) ritonavir could not be excluded.

Other side-effects associated with ribavirin are

- **Abnormal liver function tests**: In clinical trials of ribavirin in combination with different types of interferon, the majority of cases of abnormal laboratory values were managed with dose reductions. However, up to 2% of patients experienced increased ALT levels that led to dose modification or discontinuation of treatment.
- **HIV/HCV co-infection**: The overall safety profile was similar in HIV co- and mono-infection. Additional side-effects reported in co-infected patients may be related to the combination of some of the older anti-HIV drugs (no longer used) with ribavirin and pegylated interferon. In ≥1% to ≤ 2% of patients: high levels of lactate, influenza, pneumonia, fluctuating emotions, apathy, throat pain, inflamed eyes, and changes in fat distribution in the body (lipodystrophy).

**Table 16 Expected toxicities of sofosbuvir/ledipasvir with or without ribavirin**

| **Frequency** | |
|---|---|
| Very common (>10% of patients) | Fatigue and headache |
| Common (in ≥1% to <10% of patients) | Rash |

**Table 17 Expected toxicities of ombitasvir/paritaprevir/dasabuvir/ritonavir***

| **Frequency** | **ombitasvir/paritaprevir/dasabuvir/ritonavir + ribavirin N=2,044 patients** | **ombitasvir/paritaprevir/dasabuvir/ritonavir alone N = 588 patients** |
|---|---|---|
| *Blood system problems* | | |
| Common (in 1% to <10% of patients) | Anaemia | |
| *sleep problems* | | |
| Very common ( | Insomnia | |

| | | |
|---|---|---|
| in ≥10% of patients) | | |
| *stomach and gut problems* | | |
| Very common (in≥ 10% of patients) | Nausea | |
| *Skin problems* | | |
| Very common (in ≥10% of patients) | Itching of the skin | |
| Common (in 1% to <10% of patients) | | Itching of the skin |
| Rare (in ≥0.01% to <0.1%of patients) | Angioedema | Angioedema |
| *General side-effects* | | |
| Very common (experienced by 10% or more of patients) | Aches and pains<br>Fatigue | |

***the side-effect profile of ombitasvir/paritaprevir/ritonavir without dasabuvir is as listed above and in Table 17**

**Table 18 Expected toxicities of glecaprevir/pibrentasvir**

| **Frequency** | **Glecaprevir/pibrentasvir alone + ribavirin N = 78 patients** | **Glecaprevir/pibrentasvir alone N = 2265 patients** |
|---|---|---|
| *Nervous system disorders* | | |
| Very common (in ≥10% of patients) | Headache | Headache |
| *Gastrointestinal disorders* | | |
| Very common (in ≥10% of patients) | Nausea | |
| Common (in 1% to <10% of patients) | | Diarrhoea, nausea |
| *General disorders and administration site conditions* | | |
| Very common (in ≥10% of patients) | Fatigue | Fatigue |
| Common (in 1% to <10% of patients) | | Asthenia |
| *Sleep problems* | | |

| | | |
|---|---|---|
| Very common (in ≥10% of patients) | Insomnia | |
| *Blood system problems* | | |
| Common (in 1% to <10% of patients) | Anaemia | |

**Table 19 Expected toxicities of ribavirin**

| **Side-effects with ribavirin primarily in combination with interferons for HCV Patients** | | | | | |
|---|---|---|---|---|---|
| **Body system** | **Very common ≥10% of patients** | **Common 1% to <10% of patients** | **Uncommon more than 1 in 1000 people to less than 1% (1 in 100) people report it** | **Rare less than 1 in 1000 people to 1 in 10,000 people report it** | **Very rare less than 1 in 10,000 people report it** |
| Infections | | Upper respiratory infection, bronchitis, oral thrush infection, herpes simplex | Lower respiratory tract infection, pneumonia, urinary tract infection, skin infection | Infection of the heart valve, infection of the outer ear canal | |
| Blood system problems | Anaemia, low white count (neutropaenia) | Low platelets (help with blood clotting), lymphadenopathy | | Bone marrow not producing blood properly (pancytopaenia) | Aplastic anaemia |
| Immune system problems | | | Inflamed lymph nodes; inflamed thyroid gland | Anaphylaxis, autoimmune disorders – body attacking self (e.g. lupus) | Autoimmune condition affecting platelets (ITP) |
| Gland problems | | High and low thyroid function | Diabetes mellitus | | |
| General side-effects | Anorexia | | Dehydration | | |
| Psychiatric problems | Depression, insomnia | Mood alteration, emotional disorders, anxiety, aggression, nervousness, libido decreased | Suicidal ideation, hallucinations, anger | Suicide, psychosis | |
| Nervous system disorders | Headache, dizziness, decreased concentration | Memory impairment, fainting, weakness, migraine, decreased or increased sensory feeling in the skin, tingling, tremor, taste disturbance, nightmares, somnolence | Numb feet | Coma, fits, facial weakness | Stroke |

| **Side-effects with ribavirin primarily in combination with interferons for HCV Patients** | | | | | |
|---|---|---|---|---|---|
| **Body system** | **Very common ≥10% of patients** | **Common 1% to <10% of patients** | **Uncommon more than 1 in 1000 people to less than 1% (1 in 100) people report it** | **Rare less than 1 in 1000 people to 1 in 10,000 people report it** | **Very rare less than 1 in 10,000 people report it** |
| Eye disorders | | Vision blurred, eye pain, eye inflammation, dry eyes | Retinal haemorrhage | Optic nerve inflammation | Vision loss |
| Ear problems | | Vertigo, earache, tinnitus | Hearing loss | | |
| Cardiac problems | | Rapid heart rate, palpitations, swelling of the ankles | | Heart attacks, heart failure, angina, inflamed lining of the heart (pericarditis), abnormal heart rhythms (tachycardias) | |
| Vascular problems | | Flushing, hypotension | High blood pressure | Stroke, inflamed blood vessels | |
| Respiratory, problems | Shortness of breath, cough | Shortness of breath, nose bleeds, sinus congestion, nasal congestion, runny nose, sore throat | Wheezing | Inflamed lungs (resulting in death), clots on the lungs (pulmonary embolism) | |
| Stomach and gut problems | Diarrhoea, nausea, abdominal pain | Vomiting, heart burn, difficulty swallowing, mouth ulceration, bleeding gums, sore tongue and mouth, flatulence, constipation, dry mouth | Gut bleeding, gingivitis | Peptic ulcer, pancreatitis (inflamed pancreas gland) | |
| Liver problems | | | Abnormal liver function | Liver failure, inflamed gall bladder, fatty liver | |

| **Side-effects with ribavirin primarily in combination with interferons for HCV Patients** | | | | | |
|---|---|---|---|---|---|
| **Body system** | **Very common ≥10% of patients** | **Common 1% to <10% of patients** | **Uncommon more than 1 in 1000 people to less than 1% (1 in 100) people report it** | **Rare less than 1 in 1000 people to 1 in 10,000 people report it** | **Very rare less than 1 in 10,000 people report it** |
| Skin problems | Hair loss, dermatitis, itchy skin, dry skin | Rash, sweating increased, psoriasis, itchy skin rash, eczema, skin disorder, photosensitivity reaction, night sweats | | | Severe skin rashes (allergy) with peeling and ulcers, swelling of the airways |
| Musculoskeletal problems | Aching muscles, aching joints | Back pain, arthritis, muscle weakness, bone pain, neck pain, musculoskeletal pain, muscle cramps | | Inflamed muscles | |
| Reproductive system | | Impotence (difficulty getting and sustaining an erection) | | | |
| General disorders | Fevers and chills, pain, low energy, fatigue, irritability | Chest pain, influenza like illness, malaise, lethargy, hot flushes, thirst, weight loss | | | |

#### 7.3.1.E Notification

The MRC CTU at UCL should be notified of all SAEs within 24 hours of the investigator becoming aware of the event.

Investigators should notify the MRC CTU at UCL of all SAEs occurring from the time of randomisation until last follow-up. SARs and SUSARs must be notified to the MRC CTU at UCL until trial closure. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system. The MRC CTU will notify the sponsor of any SUSARs and safety issues.

### 7.3.2 NOTIFICATION PROCEDURE

1. The SAE Form must be completed by a clinician named on the Signature List and Delegation of Responsibilities Log and who is responsible for the patient's care, with due care being paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator, the form should be completed and signed by a member of the site trial team and emailed to the MRC CTU. The responsible investigator should subsequently check the SAE Form, make changes as appropriate, sign and then re-send to the MRC CTU at UCL as soon as possible. The initial report must be followed by detailed, written reports as appropriate.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of investigator reporting, the event, and why it is considered serious.

2. The SAE Form must be sent by email to the MRC CTU at UCL on mrcctu.stophcv1@ucl.ac.uk

3. Follow-up: patients must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow-up should continue after completion of protocol treatment if necessary. If further information becomes available, updates should be made to the original CRF. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and initials only. **The patient's name should not be used on any correspondence and should be deleted from any test results.**

4. Staff should follow their institution's procedure for local notification requirements.

**SAE REPORTING**
Within 24 hours of becoming aware of an SAE, please email a
completed SAE form to the MRC CTU at UCL on mrcctu.stophcv1@ucl.ac.uk
**Any CRFs sent by email must be encrypted or transferred using other secure methods**

## 7.4 MRC CTU AT UCL RESPONSIBILITIES

Medically-qualified staff at the MRC CTU at UCL or the Chief Investigator (or a medically-qualified delegate) will review all SAE reports received. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports.

The MRC CTU at UCL has been delegated the duties of trial Sponsor for reporting of SUSARs and other SARs to the regulatory authorities (MHRA) and the research ethics committee. Fatal and life-threatening SUSARs must be reported to the competent authorities within 7 days of the MRC CTU at UCL becoming aware of the event; other SUSARs must be reported within 15 days.

The MRC CTU at UCL will also keep all investigators informed of any safety issues that arise during the course of the trial.

The MRC CTU at UCL has been delegated the duties as Sponsor to submit Annual Safety Reports in the form of a Developmental Safety Update Report (DSUR) to Competent Authorities (Regulatory Authority and Ethics Committee).

# 8 QUALITY ASSURANCE & CONTROL

## 8.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This Risk Assessment has been reviewed by the Research Governance Committee (RGC) and has led to the development of a Data Management Plan (DMP), Safety Reporting Plan and Monitoring Plan which will be separately reviewed by the Quality Management Advisory Group (QMAG).

## 8.2 CENTRAL MONITORING AT MRC CTU AT UCL

MRC CTU at UCL staff will review paper CRF data for errors and missing data points. Data will be entered on to the database at MRC CTU at UCL. Data queries will be handled according to a Data Management Plan that will specify all internal data monitoring techniques employed on the study. In brief, data stored on the central database will be checked for missing or unusual values (range checks) and checked for consistency within patients over time. If any such problems are identified, the centre will be contacted and asked to verify or correct the entry. Changes will be made and entered into the database at MRC CTU at UCL. MRC CTU at UCL will send reminders for outstanding queries any overdue and/or missing data.

Other essential trial issues, events and outputs will be detailed in the Monitoring Plan that is based on the trial-specific Risk Assessment.

## 8.3 ON-SITE MONITORING

The frequency, type and intensity of routine monitoring and the requirements for triggered monitoring will be detailed in the Monitoring Plan. This plan will also detail the procedures for review and sign-off.

Monitoring will be performed at each study centre by staff from the MRC CTU at UCL. The site initiation visit or conference call will include pharmacy training, as well as the trial procedures, and procedures for handling the processing of samples. All essential site staff including the PI, lead pharmacist and lead research nurse must attend a site initiation visit/call.

The Trial Manager and/or Data Manager will visit sites to:

- verify the completeness of Investigator Site Trial Files
- confirm adherence to the protocol
- review eligibility verification and consent procedures
- verify completeness, consistency and accuracy of data being entered on CRFs
- evaluate drug accountability
- provide additional training as needed.

The monitors will require access to all patient medical records including, but not limited to, laboratory test results and prescriptions. The site Principal Investigator (or delegated deputy) will work with the monitor to ensure that any problems detected are resolved. Relevant trial documentation will be retained for 15 years.

### 8.3.1 DIRECT ACCESS TO PATIENT RECORDS

Participating investigators should agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Patients' consent for this must be obtained. Such information will be treated as strictly confidential and will in no circumstances be made publicly available.

### 8.3.2 CONFIDENTIALITY

We will follow the principles of the UK DPA.

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorised parties. Patients will be assigned a trial identification number and this will be used on CRFs; patients will not be identified by their name on CRFs. With permission, patient NHS numbers will be collected; these will be linked only to the patient's trial number in a separate database. The reason for collecting NHS number is, so that long-term follow-up for hepatitis C related events (eg hepatocellular carcinoma) can be obtained by authorised persons. The investigator will keep securely a patient trial register showing identification numbers, surnames and date of birth. This unique trial number will identify all laboratory specimens, case record forms, and other records and no names will be used, in order to maintain confidentiality. Clinical information will not be released without written permission, except as necessary for monitoring, auditing and inspection purposes.

Any CRFs that are scanned and sent by email (rather than post) must be encrypted or transferred using other secure methods.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 METHOD OF RANDOMISATION

Because of the number of sites randomisation will be computer-generated at MRC CTU at UCL using a minimisation algorithm incorporating a probabilistic element. Allocation will be concealed until the point of the next randomisation. Randomisation will not take place until after informed consent has been given and the patient is ready to receive therapy. Authorised individuals (according to the Signature List and Delegation of Responsibilities Log) at each site can carry out randomisation by contacting the MRC CTU at UCL.

The randomisation will be implemented as a pure factorial, that is individuals randomly assigned to any one of four groups (fixed vs varying; adjunctive ribavirin or not). To accommodate the partial factorial, those receiving glecaprevir/pibrentasvir will be considered randomised to 8 weeks treatment without ribavirin (i.e. the ribavirin randomisation will be ignored in these groups). This preserves the 1:1 randomisation to fixed:varying duration overall.

## 9.2 OUTCOME MEASURES

### 9.2.1 PRIMARY OUTCOME MEASURE

#### 9.2.1.A Biomarker-stratified duration comparison

The primary outcome for the biomarker-stratified duration comparison is the proportion of patients in each randomised group who achieve SVR12 following first-line and re-treatment (where necessary), ie SVR12 across the treatment/re-treatment pathway ('overall SVR12').

Sustained Virological Response (SVR) is defined as undetectable plasma (HCV RNA <LLOQ) measured 12 weeks after the end of treatment (first line +/- re-treatment) without failure defined as either:

i. two consecutive measurements of HCV RNA > LLOQ (taken at least one week apart) after two consecutive visits with HCV RNA <LLOQ, at any time, with the latter confirmatory measurement also being >2000 IU/ml
ii. two consecutive measurements of HCV RNA (taken at least one week apart) that are >1 $\log_{10}$ increase above HCV RNA nadir on treatment and >2000 IU/ml, at any time.

Thus for patients who do not fail on first-line (and are not re-treated), this will be SVR12 after first-line treatment; for those who fail on first-line and start re-treatment this will be SVR12 after re-treatment; any patient who fails on first-line but chooses not to be re-treated will be counted as a failure.

For the vast majority of patients with SVR12, their HCV RNA 8 weeks post-EOT will also have been undetectable (ie SVR12 will be confirmed). Any patient whose HCV RNA is >LLOQ for the first time 12 weeks post EOT should have a second test performed at least one week later to confirm failure. Such patients will be conservatively assumed to not have achieved SVR12, regardless of the value of the confirmatory test, but should continue to be followed closely.

Many studies have shown very high associations between SVR12 and SVR24. The latter was used historically to define cure. SVR12 is now the accepted outcome measure for regulatory trials[42]. Durable SVR (at either 12 or 24 weeks) has been shown across many studies to have long term benefits on clinical outcomes including all-cause mortality, progression of liver disease and hepatocellular carcinoma (HCC)[7].

#### 9.2.1.B Ribavirin comparison

For the ribavirin comparison, the primary outcome is the proportion of patients in each randomised group who achieve SVR12 following first-line treatment, assessed 12 weeks after end of treatment (first-line SVR12).

The reason for focusing on first-line cure for the ribavirin comparison is that the hypothesis is that adjunctive ribavirin will be superior, ie increase cure rates, and that re-treatment will be successful in curing all patients who fail first-line. Therefore the primary interest is in the impact of ribavirin on first-line cure.

### 9.2.2 SECONDARY OUTCOME MEASURES

Secondary outcomes for all randomised comparisons (where not the primary outcome measure) are:

1. Proportion of patients achieving SVR12 following first-line therapy (stratified duration comparison)
2. Proportion of patients achieving SVR12 overall following first-line plus re-treatment therapy (ribavirin comparison)
3. Sustained virological response 24 weeks after completion of all therapy (overall SVR24)
4. Sustained virological response 24 weeks after completion of first-line therapy only (first-line SVR24)
5. Proportion of patients with primary first-line treatment failure (confirmed >1 $\log_{10}$ increase from HCV RNA nadir on treatment and >2000 IU/ml)
6. Viral load rebound (HCV RNA > LLOQ) after two consecutive visits with HCV RNA <LLOQ with the latter confirmatory measurement also being >2000 IU/ml (on first-line therapy and after stopping first-line therapy)
7. Proportion with detectable HCV viral load 4 weeks after randomisation
8. Proportion of patients with one or more serious adverse events (SAEs)
9. Proportion of patients with one or more severe (grade 3/4) adverse events (AEs)
10. Proportion of patients with one or more grade 3/4 AEs judged definitely/probably related to one or more study medications
11. Proportion of patients requiring any change to study medication because of AEs
12. Proportion of patients with grade 3/4 anaemia
13. Proportion of patients with emergent resistance associated variants (RAVs)
14. Overall total treatment cost, and treatment cost per cure
15. Sensitivity and specificity of Epistem diagnostic platform for detecting presence of IL28T allele

Methods to protect against bias include the use of a "failure" primary outcome measure which is based on a laboratory test and therefore not subject to clinical opinion. The test (HCV viral load) is widely used in clinical practice, and all centres in the trial use laboratories that participate in external quality assurance programs. Randomisation will be stratified by centre, so that even if there are very small differences between laboratories, these will not bias the randomised comparison. All patients will follow the same visit schedule after end of treatment, ensuring that measurement frequency is identical.

## 9.3 SAMPLE SIZE

The trial is powered to demonstrate

- non-inferiority of biomarker-stratified (varying) 4-7 week first-line treatment followed by 12 weeks re-treatment versus fixed 8 week first-line treatment with the same re-treatment.

- superiority of adjunctive ribavirin in first-line treatment

The primary endpoint for the non-inferiority comparison is **overall SVR12 after first-line and re-treatment** (where necessary), which we estimate at **98% for the control group** regardless of first-line combination, given the very high cure rates achieved with the 12 week ribavirin-containing regimens that will be used for re-treatment, and the limited impact of prior DAAs treatment on response to subsequent regimens.

As an example, from previous trials[26], we can assume 96% and 84% SVR12 with 8 weeks ombitasvir/paritaprevir/dasabuvir/ritonavir in genotype 1b and 1a respectively. With a 1:2 ratio of presenting cases (reflecting UK prevalence[43]), the cure rate in the control first-line group would be 88% prior to re-treatment. Conservatively assuming a cure rate of re-treatment of 85% to allow for potential role of mutations, particularly in NS5a, would lead to overall 98% cure in the control group. However, similar overall 98% cure rates could be achieved with lower first-line and higher re-treatment cure rates (e.g. 65% first-line, 94% re-treatment) or higher first-line and lower re-treatment cure rates (e.g. 95% first-line, 60% re-treatment). Whilst first-line cure rates may be slightly lower or higher with 8 weeks of different first-line combinations (in particular first-line cure rates might be expected to be higher with 8 weeks glecaprevir/pibrentasvir since this is the licenced indication, albeit without much real-world experience to date), in practice it is unlikely that an overall cure rate of 98% from first-line plus re-treatment can be exceeded, so the control group rate of 98% is reasonable across different first-line regimens.

Assuming a 98% cure rate overall for the control group, for a 4% non-inferiority margin, 80% power and one-sided $\alpha$=0.025 the required sample size for the biomarker-stratified duration comparison is **408 patients**, allowing for 5% early withdrawal (primary outcomes will be imputed).

The 4% non-inferiority margin is arbitrary, but ensures that overall cure rates in the biomarker-stratified short-course group would be well over 90% if the trial were to declare non-inferiority. Further, even small genuine reductions in overall cure rate with short-course treatment substantially decrease the trial's power to demonstrate non-inferiority (from 80% to 52%, 25% and 11% of short-course genuinely achieves overall cure rates that are 1%, 2% or 3% lower, respectively).

If non-inferiority is not demonstrated, 408 patients is likely to provide reasonable power to investigate other predictors of cure, such as presence of viral quasispecies including resistance, age (related to immune health), IL28 polymorphisms, and BMI.

The sample size for the fixed vs duration non-inferiority comparison is conducted under the null hypothesis for the ribavirin superiority comparison (i.e. no effect). Given its partial factorial nature, estimates of the effect of adjunctive ribavirin will be determined from generalised linear models which include terms to reflect the randomisations and the specific first-line DAA regimen received, so that patients randomised to 8 weeks' glecaprevir/pibrentasvir effectively do not contribute to this comparison. We estimate that this will be approximately 25% of patients (102). 306 patients randomised to adjunctive ribavirin or not provides 75-85% power to identify a 10% improvement in first-line cure rate associated with adjunctive ribavirin for first-line cure rates 83-86% without and 93-96% with ribavirin (two-sided alpha=0.05) and >80% power to identify a 15% improvement in first-line cure rate associated with adjunctive ribavirin for first-line cure rates 60-80%, allowing for 5% early withdrawal as above (primary outcomes will be imputed).

## 9.4 INTERIM MONITORING & ANALYSES

A DMC Charter will be drawn up that describes the membership of the DMC, relationships with other committees, terms of reference, decision-making processes, and the timing and frequency of interim analyses (with a description of stopping rules and/or guidelines, if any). The DMC will meet approximately 6-monthly. See **Section 13.3**.

### 9.4.1 PRE-SPECIFIED ADAPTATION

In particular, whilst the inclusion of re-treatment phase means that, overall, every patient has a very high probability of achieving cure (estimated at 98%), it is possible that the first-line cure rate with the biomarker-stratified short-course is substantially lower than the anticipated 88-90%. If, as an extreme example (highly unlikely given data on short-course treatment to date), first-line cure rates with biomarker-stratified short-course treatment were as low as 20%, there would be little value in continuing the trial, even if overall 98% of patients achieved cure with re-treatment.

The most plausible reason for lower than expected first-line cure rates with biomarker-shortened first-line treatment is that this strategy will not be successful in those with higher screening HCV VLs. We therefore pre-specify an adaptation to the trial that could be recommended by the DMC, namely **to change the eligibility criteria to lower the viral load threshold for the study.** This threshold would be determined by the DMC from a subgroup analysis investigating interaction between biomarker-stratified duration and baseline HCV VL as a continuous factor (incorporating non-linearity in interaction effect using natural cubic splines). This would be performed if there is strong evidence that the first-line response rate in those randomised to biomarker-stratified short-course treatment is less than 65% (based on the upper limit of the 99.9% CI) (**Table 20**). In this instance, the DMC could also recommend an overall increase to the number of sample size to provide 408 patients meeting the revised eligibility criteria in whom to determine non-inferiority at the end of the trial. The DMC could also change the different HCV VL thresholds determining the short-course duration (**Table** 12) because simply reducing the screening HCV VL threshold might lead to little variation in days of treatment received. This would be done following the same strategy as used to define the planned biomarker-stratification (modelling of declines in HCV VL on treatment), but using data on actual VL declines in the trial to date.

**Table 20 First-line cure rates leading to an adaptation in eligibility criteria**

| Number enrolled in short-course group | Minimum number cured such that 99.9% CI around the proportion cured is lower than 65% | Proportion cured at this minimum | Upper 99.9% CI limit around this proportion cured |
|---|---|---|---|
| 10 | 1 | 0.10 | 0.65 |
| 20 | 5 | 0.25 | 0.64 |
| 30 | 11 | 0.37 | 0.68 |
| 40 | 16 | 0.40 | 0.67 |
| 50 | 21 | 0.42 | 0.66 |
| 60 | 26 | 0.43 | 0.65 |
| 70 | 31 | 0.44 | 0.64 |
| 80 | 37 | 0.46 | 0.65 |
| 90 | 42 | 0.47 | 0.64 |
| 100 | 48 | 0.48 | 0.65 |
| 110 | 55 | 0.50 | 0.66 |
| 120 | 60 | 0.50 | 0.65 |

| | | | |
|---|---|---|---|
| 130 | 65 | 0.50 | 0.64 |
| 140 | 71 | 0.51 | 0.65 |
| 150 | 77 | 0.51 | 0.65 |
| 160 | 83 | 0.52 | 0.65 |
| 170 | 89 | 0.52 | 0.65 |
| 180 | 95 | 0.53 | 0.65 |
| 190 | 100 | 0.53 | 0.65 |
| 200 | 107 | 0.54 | 0.65 |

## 9.5 ANALYSIS PLAN (BRIEF)

The analyses will be described in detail in a full Statistical Analysis Plan. This section summarises the main issues.

Analysis would be intention-to-treat, including all patients in their originally randomised group regardless of treatment received. Primary analysis of SVR12 would be as observed (those discontinuing first-line treatment early and not undergoing re-treatment with detectable HCV RNA 12 weeks later counted as failures). Any missing data at 12 weeks post EOT due to assay failure or missed visit would be multiply imputed within treatment group based on all viral load measurements and baseline characteristics, using chained estimating equations. Continuous variables would be transformed for normality, and data augmented following standard recommendations to avoid problems with perfect prediction. The distribution of imputed data would be checked versus observed data.

As the primary biomarker-stratified duration comparison is non-inferiority, secondary analyses would be based on a per-protocol population, which we (arbitrarily) define as receiving >90% and <110% of the prescribed duration of first-line treatment (+/- ribavirin), and where the difference between screening and enrolment HCV RNA values would have led to a difference of ≤2 days in allocated duration of DAAs had they been allocated to the varying duration group. Assessment of treatment received will be based on both prescription and adherence assessed by pill counts performed every 2 weeks (whilst on treatment).

A further secondary analysis will exclude reinfections leading to rebound virus, with reinfection determined by genotype and full genome sequencing.

As the duration of follow-up is relatively short, primary analysis would consider outcomes as binary. Risk differences between groups, and their 95% CI, would be estimated using binomial regression on the risk difference scale using a generalised linear model as that is the scale on which the non-inferiority margin is pre-specified.. However, in case of non-convergence due to closeness to the boundary (cure probability equalling 1) the risk ratio scale will also be considered. The non-inferiority margin for the primary comparison for the biomarker-stratified randomisation is 4%; the stratified treatment duration will be considered non-inferior if the 95% CI for the difference between intervention vs control lies above 4%. This will ensure that, if non-inferiority is concluded, then the overall cure rate in the biomarker-stratified intervention group will be well above 90%. It is important to note that the entire 95% confidence interval must lie above this 4% lower bound to conclude non-inferiority. In practice, it becomes increasingly difficult to achieve this with even small increases in failure rates in the intervention group. Simulations demonstrate that if the overall failure rate in the control group is 2%, then if the intervention group failure rate is only 1% higher, at 3% overall, then the power drops to just 52% (ie in only 52% of simulations is the entire 95% CI

above the non-inferiority margin). If the failure rate is genuinely 4% (2% higher), only 25% of simulations would declare non-inferiority. Interactions between the different randomisations will be investigated, and results presented in each subgroup with heterogeneity tests. Secondary analyses will use Bayesian methods to directly estimate the probability that each intervention regimen is 1%, 2%, 3%, 4% etc worse than control. Secondary analyses of viral suppression and rebound would use time-to-event methods (Kaplan-Meier, Cox regression).

Primary analyses of outcomes restricted to first-line therapy will stratify by the first-line DAA duration received (protocol v4.0 or earlier vs protocol v5.0 or later) and by first-line regimen by including these terms as main effects, together with randomised group (with and without interactions between randomised group). The primary analysis for the primary outcome (first-line and re-treatment) will be unstratified, reflecting the original protocol and the overall strategy comparison: secondary analysis of the primary outcome will be conducted stratified as for first-line outcomes.

### 9.5.1 PLANNED SUBGROUP ANALYSES

In addition to the other randomisations, planned sub-group analyses include

- baseline HCV VL (treated as a continuous interaction, but also considering a dichotomisation at 6,000,000 IU/ml)
- genotype 1a vs 1b vs 4
- presence of viral quasispecies including resistance
- age (related to immune health)
- sex
- HIV co-infection
- IL28 polymorphisms
- BMI
- Early HCV RNA treatment responses, to days 3, 7 and 14
- previous (failed) treatment with interferon-alpha with/out ribavirin, overall and according to whether patients were intolerant relapsers, relapsers after full treatment or non-responders
- duration strategy (protocol v4.0 or earlier vs protocol v5.0 or later)
- first-line regimen.

## 9.6 COST-EFFECTIVENESS ANALYSIS

We will conduct a cost effectiveness analysis of DAA therapy in the NHS, informed by the results of the trial. Due to the limited trial follow-up period, we propose a framework based on decision analysis. Such an approach allows including findings from the trial in the context of the existing evidence on all treatments of interest and is the preferred approach for societal decision making in the UK.

Analyses will be built based on the requirements of the National Institute of Health and Care Excellence[44]. The analysis will adopt a consistent perspective on costs (NHS/Personal Social Services Unit), and health effects will be expressed in terms of quality-adjusted life-years (QALYs). All economic analyses will be by intention-to-treat. A decision model will be developed with the aid of clinicians. By developing a model that adequately describes both the short and longer term consequences, we anticipate providing a full assessment of the impact on quality adjusted survival duration and costs of the alternative treatments. To inform such analyses further evidence will be sought in the published literature, but this will focus on reviews rather than on primary sources, i.e. reviews of reviews. The evidence will be synthesised, if needed, for inclusion in the model.

The cost-effectiveness of alternative treatments will be represented using incremental cost effectiveness ratios (ICER) for each strategy evaluated. The decision to adopt one treatment strategy, rather than another, will be determined by comparing the ICERs to threshold values for the cost of an additional unit of benefit (NICE uses a threshold of £20,000 to £30,000 per QALY gained), using a full incremental analysis[44].

Uncertainty will be evaluated using probabilistic sensitivity analysis based on Monte Carlo simulation[45]. Decision uncertainty will be characterised by an evaluation of the probability of each strategy being cost effective, for a range of threshold costs of an additional QALY. Cost effectiveness acceptability curves (CEACs) can be use to display such information in a plot[46,47]. We also aim to explore patient heterogeneity by performing subgroup analysis. Relevant subgroups for analysis will be defined from the ones used in the clinical effectiveness analysis.

# 10 REGULATORY & ETHICAL ISSUES

All regulatory requirements (including safety reporting, see **Section 7** (p62) and below) will be met by the sponsor or their delegated authorities.

## 10.1 COMPLIANCE

### 10.1.1 REGULATORY COMPLIANCE

The trial complies with the principles of the current version of the Declaration of Helsinki.

It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 (The Medicines for Human Use [Clinical Trials] Regulations 2004) and subsequent amendments, the UK Data Protection Act (DPA number: Z5886415), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

### 10.1.2 SITE COMPLIANCE

All sites will comply with the above. An agreement will be in place between each site and the MRC CTU at UCL, setting out respective roles and responsibilities (see **Section 12 - Finance**).

The site will inform the Trials Unit as soon as they are aware of a possible serious breach of compliance, so that the Trials Unit can report this breach if necessary within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants in the trial, or
- The scientific value of the trial

### 10.1.3 DATA COLLECTION & RETENTION

CRFs, clinical notes and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for 15 years after the end of the trial. During this period, all data should be accessible to the competent or equivalent authorities, the Sponsor, and other delegated authorities with suitable notice. The data may be subject to an audit by the competent authorities.

## 10.2 ETHICAL CONDUCT OF THE STUDY

### 10.2.1 ETHICAL CONSIDERATIONS

As the drugs to be used in the trial are licensed for the indication, and written, informed consent will be obtained from all patients, the main ethical issues relate to ensuring that patients are fully informed about the research and the risk and benefits of participating for them. We have ensured that the information for patients is clear and understandable by developing it in collaboration with our patient representatives. All trial documentation will stress the voluntary nature of participation and full information will be provided to potential patients on all relevant study procedures, the right to withdraw without explanation and without any resulting detriment in clinical care.

Eligible patients will be identified at participating centres by clinicians and investigators involved in their routine care. Patients will have to provide individual informed consent to take part; no incapacitated patients will be recruited. As HCV is a chronic condition, all patients will be provided with at least 24 hours to consider participation. The delegation log at each trial centre will clearly identify investigators who are able to take informed consent; this may vary between different NHS Trusts (eg in terms of who can take consent), but will follow local procedures.

Patients will be provided with payment to cover their travel costs and time for three research visits in the initial treatment phase (£50 per visit) and any retreatment visits (£25 per visit).

### 10.2.2 ETHICAL APPROVALS

Before initiation of the trial at each clinical site, the protocol, all informed consent forms, and information materials to be given to the prospective patient will be submitted to the ethics committee for approval. Any further amendments will be submitted and approved by the ethics committee.

The rights of the patient to refuse to participate in the trial without giving a reason must be respected. After the patient has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. The reason for doing so, however, should be recorded; the patient will remain within the trial for the purpose of follow-up ("off study drug, on study") and for data analysis by the treatment option to which they have been allocated. Similarly, the patient must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his/her further treatment.

## 10.3 COMPETENT AUTHORITY APPROVALS

This protocol will be reviewed by the MHRA.

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK. The EUdraCT number for the trial is **2015-005004-28.**

The progress of the trial and safety issues will be reported to the competent authority, regulatory agency or equivalent in accordance with local requirements and practices in a timely manner.

Safety reports, including expedited reporting and SUSARS will be submitted to the competent authority in accordance with each authority's requirements in a timely manner.

## 10.4 OTHER APPROVALS

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required. A copy of the local R&D approval (or other relevant approval as above) and of the PIS and Consent Form (CF) on local headed paper should be forwarded to the MRC CTU at UCL before patients are entered.

## 10.5 TRIAL CLOSURE

The trial will close when all patients have completed follow-up (24 weeks after last EOT visit).

## 10.6 SHARING OF SAMPLES AND DATA

Funders and journals increasingly support the publication of full underlying data in order to maximise the use of data generated through publicly funded research. Therefore pseudo-anonymised data from this study may be shared worldwide. Only study number and year (not date) of birth would be shared in this way (not name, initials or NHS number), together with information on treatment received and outcomes, and HCV virus sequence.

Samples will be stored for at least 30 years, initially in the UK. After the end of the trial, samples may be shipped to the UK, North America or Europe, depending on where the research groups who develop new tests are based.

The Patient Information Sheet includes details on sharing of data and samples. Patients who withdraw may refuse consent for samples previously collected in the trial to be used (see **Section 6.5**).

# 11 INDEMNITY

The sponsor of the study, Imperial College, holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this study.

If it can be demonstrated that a participant experienced serious and enduring harm as a result of their participation in this study, they may be eligible to claim compensation without having to prove that Imperial College is at fault. If the injury resulted from any procedure which is not part of the study, Imperial College will not be required to compensate them in this way. Their legal rights to claim compensation for injury where it can be proven as negligence are not affected.

# 12 FINANCE

The trial is supported by grant funding from the Efficacy and Mechanism and Evaluation Programme, an MRC and NIHR partnership (14/02/17).

The trial will be coordinated by the MRC CTU at UCL. A written agreement with the NHS Trust or Board of each site principal investigator (PI) and the MRC CTU at UCL will set out the obligations of the parties to the agreement, their respective roles and responsibilities and cover arrangements for budgets and financial transfers and reporting. The study will also be registered through the NIHR portfolio system for adoption by the CRN.

# 13 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in the figure.

## 13.1 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the MRC Clinical Trials Unit (CTU). The TMG will be responsible for the day-to-day running and management of the trial. It will meet approximately three times a year at least one of which will be in-person. The full details can be found in the TMG Charter.

## 13.2 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) has membership from the TMG plus independent members, including the Chair. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.

## 13.3 DATA MONITORING COMMITTEE (DMC)

An independent Data Monitoring Committee (DMC) will be formed. The DMC will be the only group who sees the confidential, accumulating data for the trial. Reports to the DMC will be produced by the MRC CTU at UCL statisticians. The DMC will meet within 6 months of the trial opening; the frequency of meetings will be dictated in the DMC charter. The DMC will consider both clinical and statistical evidence using the statistical analysis plan (see **Section 9.5**) and will advise the TSC. Statistical evidence would be based on the Haybittle-Peto rule ($p<0.001$ for difference between randomised groups): this has the advantage that the number of DMC meetings does not have to be pre-specified in advance, and the DMC can meet more frequently as determined by the data. The DMC would consider both the primary outcome measure of overall cure (first-line plus re-treatment) and first-line cure alone in their deliberations regarding trial stopping. The DMC can recommend premature closure or reporting of the trial, or that recruitment to any research group be discontinued, or changes to eligibility criteria. See **Section 9.4.1** for pre-specified adaptation.

Further details of DMC functioning, and the procedures for interim analysis and monitoring are provided in the DMC Charter.

## 13.4 ROLE OF STUDY SPONSOR

Neither the study sponsor nor the funders will have or had any role in study design, data collection, management, analysis, writing of the study report or the decision to submit for publication.

# 14 PUBLICATION

The TSC is the custodian of the data and specimens generated from the STOP-HCV-1 trial; STOP-HCV-1 trial data are not the property of individual participating investigators or health care facilities where the data were generated. However, the patient samples and the host DNA/RNA collected from a centre and stored within the STOP-HCV-1 trial cannot be used for investigations not described in this protocol without the written permission of that centre's PI.

We anticipate there will be wide interest in the final trial results with publication in a major medical journal. Investigators will promote dissemination of results widely across the NHS and ensure their maximal influence on clinical care. The results will also be disseminated to the public and patients through the Hepatitis Trust.

However, it is anticipated that there may be opportunities for publication during the course of the STOP-HCV-1 trial (not by randomised group). Publications include abstracts and oral/poster presentations for national and international meetings, as well as manuscripts for peer-reviewed journals. In order to avoid disputes regarding authorship, it is important to establish a consensus approach that will provide a framework for all publications derived in full or in part from this clinical trial. The following approach is derived from the *Lancet* and from the publication policies used in other MRC clinical trials:

- All publications are to be approved by the TMG and TSC before submission for publication. Any publication arising before the end of the trial (not by randomised groups) will also be approved by the DMC in order to ensure that the primary objective of the trial (the randomised comparison) is not compromised. In particular, no analyses by randomised group of any outcome (primary, secondary or other) in either the main trial or associated substudies will be conducted or presented before the end of the trial, other than those for interim review by the DMC. The TMG and TSC will resolve problems of authorship and maintain the quality of publications.

- In line with NIHR policy that the results of publicly-funded research should be freely available, manuscripts arising from the trial will, wherever possible, be submitted to peer-reviewed journals which enable Open Access via UK PubMed Central (PMC) within six months of the official date of final publication. All conference presentations will be made available as soon as possible after the event via the STOP-HCV-1 website. All publications will acknowledge the trial's funding sources.

- For all publications, the TMG will nominate a chairperson or approve an individual's request to chair a manuscript writing committee. The chair will usually be the primary or senior author. The chairperson is responsible for identifying fellow authors and for determining with that group the order of authorship that will appear on the manuscript. The TSC will resolve any problems of authorship and maintain the quality of publications.

- The TMG will maintain a list of investigators to be presented in an appendix at the end of the paper. This list will include investigators who contributed to the investigation being reported but who are not members of the writing committee. In principle, substudy reports should include all investigators for the main study, although in some instances where a smaller number of investigators have made any form of contribution, it may be appropriate to abbreviate the listing. All headline authors in any publication arising from the main study or sub-studies must have a made a substantive academic or project management contribution to the work that is

being presented. "Substantive" must be defined by a written declaration of exactly what the contribution of any individual is believed to have been. In addition to fulfilling the criteria based on contribution, additional features that will be considered in selecting an authorship group will include the recruitment of patients who contributed data to any set of analyses contained in the manuscript and/or the conduct of analyses (laboratory and statistical), leadership and coordination of the project in the absence of a clear academic contribution.

- The data derived from this clinical trial are considered the property of the Chair of the TSC. The presentation or publication of any data collected by the participating investigators on patients entered into this trial is under the direct control the TMG and TSC (and the DMC before the end of the trial). This is true whether the publication or presentation is concerned directly with the results of the trial or is associated with the trial in some other way. However, although individual participating investigators will not have any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any of the data other than under the auspices of and with the approval of the TMG and TSC (and the DMC before the end of the trial), they will be encouraged to develop sub-studies or propose analyses subject to the approval by the TMG and TSC (and the DMC before the end of the trial). Any requests for access to raw data will be welcomed as long as they are scientifically valid and do not conflict with the integrity of the trial or ongoing analyses by the trial team.

- Outcome data by randomised group will not be revealed to the participating investigators until the data collection phase and primary full analysis of the trial has been completed. This policy safeguards against possible bias affecting the data collection. The DMC will be monitoring the outcome results and may recommend that the trial be stopped for safety reasons or if a definitive answer is reached earlier than the scheduled end of the trial.

# 15 PROTOCOL AMENDMENTS

| **Protocol v1.0 12-Dec-2015 approved by REC 29-Dec-2015 and MHRA 31-Dec-2015** | |
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| **Protocol v2.0 19-Jan-2016 approved by REC 10-Feb-2016 and MHRA 01-Feb-2016** | |
| **Changes made** | **Sections updated** |
| Wording in the Summary of Trial has been made consistent with the inclusion criteria.<br><br>Previous wording: Patients co-infected with HIV are eligible if HIV viral load has been <50 copies/ml for >24 weeks on anti-HIV drugs with no interactions with study interventions.<br><br>New wording: *Patients co-infected with HIV are eligible if HIV viral load has been <50 copies/ml for >24 weeks on anti-HIV drugs*. | Summary of Trial |
| Following review by the MHRA the study was authorised subject to a substantial amendment being submitted to clarify the definition of "sexual abstinence" as a method of contraception in the protocol.<br><br>Previous wording: Sexual abstinence where this involves refraining from heterosexual intercourse during the entire period of risk.<br><br>New wording**:** *Sexual abstinence where this involves refraining from heterosexual intercourse during the entire period of risk. For sexual abstinence to be acceptable as an effective contraception abstinence must be specified as the preferred and usual lifestyle of the patient*. | 3.6 Contraception |
| Clarification on the definition of failure on first-line treatment.<br><br>Previous wording: Two consecutive measurements of HCV RNA > LLOQ (taken at least one week apart) after two consecutive visits with HCV RNA <LLOQ at any time.<br><br>New wording**:** *Two consecutive measurements of HCV RNA > LLOQ (taken at least one week apart) after two consecutive visits with HCV RNA <LLOQ at any time, with the latter confirmatory measurement also being >2000 IU/ml.* | 5.2 Definition of failure on first line treatment and move to re-treatment<br><br>9.2.1.A Within trial biomarker-stratified duration comparison<br><br>9.2.2 Secondary Outcome Measures |
| Changes have been made to be consistent with the clarifications made to the definition of first-line treatment failure.<br><br>Previous wording: Therefore any patient with a single HCV RNA >LLOQ after confirmed HCV RNA <LLOQ, or with a single value >2000 IU/ml and >1 log10 increase above the HCV RNA nadir on treatment should be recalled for a second HCV RNA test at least one week after the initial value to confirm whether or not failure | Table 1 Trial Assessment Schedule – first line treatment<br><br>5.2 Definition of failure on first line treatment and move to re-treatment |

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| has occurred.<br><br>New wording**:** *Therefore any patient with a single HCV RNA >LLOQ after two consecutive HCV RNA <LLOQ, or with a single value >2000 IU/ml and >1 log10 increase above the HCV RNA nadir during treatment or post-end of treatment, should be recalled for a second HCV RNA test at least one week after the initial values to confirm whether failure has occurred or not***.** | |
| Clarification on the dose modification, interruptions and discontinuation of Viekirax due to hepatic impairment.<br><br>Previous wording: If the patient develops symptomatic hepatitis or remains asymptomatic but with increasing ALT levels, all HCV drugs must be ceased. Re-challenge must not occur until the case is discussed with the TMG. It is recommended that asymptomatic patients experiencing ≥ 5 x ULN elevations of ALT are monitored more closely with weekly ALT testing until resolution.<br><br>New wording: *If the patient develops symptomatic hepatitis, or remains asymptomatic but with ALT ≥ x 10 ULN and the investigator believes this could possibly be related to drug all HCV drugs should be ceased. Re-challenge must not occur until the case is discussed with the TMG. It is recommended that asymptomatic patients experiencing ≥5 x ULN elevations of ALT are monitored more closely with weekly ALT testing until resolution.* | 5.3.5.A Hepatic Impairment |
| Correction of the HCV VL interval to match with the stipulated inclusion criteria.<br><br>Previous wording: interval between 1,000 – 300,000<br><br>New wording: *interval between the LLOQ – 300, 000* | Table 9 Duration of first line treatment in the intervention biomarker-stratified group |
| The version of the Medical Outcomes Study Short-Form 12 (SF-12) has been changed to reflect the correct version that will be used in the study.<br><br>Previous wording: version 1<br><br>New wording: *version 2* | Table 1 Trial Assessment Schedule – first line treatment footer<br><br>Table 2 Trial Assessment Schedule – Re-treatment<br><br>6.4 Other Assessments |
| Protocol version number and date updated on first page and on all page headers. | |
| **Protocol v3.0 04-Apr-2016 approved by REC 29-Apr-2016 and MHRA 18-May-2016** | |
| **Changes made** | **Sections updated** |
| The trial assessment schedule has been updated to clarify the storage sample requirements for the study. The storage sample collection element which was part of the original table has been separated from the other trial assessments and clarification of the options available for sample storage has been provided. | Table 1. Trial Assessment Schedule – first-line treatment real-time tests<br><br>Table 2. Sample Collection Schedule – first-line treatment sample storage<br><br>Table 3. Trial Assessments and Sample Collection Schedule – Re-treatment |

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| The footer note on the trial assessment schedule has been updated to confirm that sites are able to use screening CD4 cell counts from within 1 year of randomisation day. | Table 1. Trial Assessment Schedule – first-line treatment real-time tests |
| The ISRCTN Registration number has also been added to the protocol. | Cover page |
| Protocol version number and date updated on first page and on all page headers. | |
| **Protocol v4.0 24-Oct-2016 approved by REC 07-Nov-2016 and MHRA 30-Nov-2016** | |
| **Changes made** | **Sections updated** |
| Updates to the MRC CTU Staff | Trial Administration<br>Summary of Trial |
| Secondary outcome measures have changed to capture grade 3/4 AEs judged definitely/probably related to study medications.<br>Previous wording: AEs of any grade<br>New wording: *grade 3/4 AEs* | Summary of Trial<br>Trial Schema Figure 1<br>9.9.2 Secondary Outcome Measures |
| Site requirements for reporting adverse reaction of any grade has been changed:<br>Previous wording: reactions (any grade), grade 3 or 4<br>New wording: *grade 3 or 4 adverse events or reactions* | 6.3 Procedures for Assessing Safety<br>7.1.5 Other Study-Specific Requirements<br>7.3 Investigator Responsibilities |
| Full drug name for ritonavir added to Trial Schema<br>Previous wording: r<br>New wording: *ritonavir* | Trial Schema Figure 1 |
| Footnotes have been added to the Trial Assessment Schedule – first line:<br>1) New wording: *EPISTEM test can be done at any time point if not possible on day 0.*<br>2) New wording: *If a participant is hard to bleed, the blood tests should be prioritised as follows: HCV viral load>biochemistry>haematology (FBC>differential>INR) >coagulation markers> storage.*<br>3) New wording: *If unable to bleed on day 28, EOT or post-EOT week 12, the patient should be recalled, as these are critical visits for clinical care.* | Table 1 Trial Assessment Schedule – first line treatment real-time tests |
| The Sample collection schedule was updated to clarify what is required for sites using DX shipment to Glasgow:<br>Previous wording: EDTA plasma for DX to Glasgow<br>New wording: *EDTA whole blood for DX to Glasgow* | Table 2 Sample collection schedule – first line treatment sample storage |
| Footnotes have been added to the Sample Collection | Table 2 Sample collection schedule – first |

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| Schedule:<br>1) New wording: *Can be taken at any time point if not possible on day 0.*<br>2) New wording: *If day 0 taken, up to a maximum of 4 other timepoints will be collected with EOT being most important. The collection on day 0 can be taken at either screening or day 0.* | line treatment sample storage |
| 5ml EDTA whole blood collection has been separated into 2 rows and the footnote removed on the Sample Collection Schedule:<br>Old wording: Whole blood for DNA storage for DX to Glasgow (5ml)<br>New wording: *EDTA whole blood for DNA storage for DX to Glasgow (2.5ml)*<br>*Whole blood in PAXgene blood RNA tube (Qiagen) for DX to Glasgow (2.5ml)*<br>Old wording: [Footer] 2.5ml into EDTA and 2.5ml into PAXgene blood RNA tube (Qiagen). Store EDTA blood for later DNA extraction and PAXgene tube for later RNA extraction. | Table 2 Sample Collection Schedule – first line treatment sample storage |
| Crosses eliminated under time points for remnant plasma samples where a sample is already sent to Glasgow. | Table 2 Sample collection schedule – first line treatment sample storage<br>Table 3 Trial Assessments and Sample Collection Schedule – Re-treatment |
| Footnotes have been added to Trial Assessments and Sample Collection Schedule:<br>1) New wording: *If a participant is hard to bleed, the blood tests should be prioritised as follows: HCV viral load>biochemistry>haematology (FBC>differential>INR)>coagulation markers>storage.*<br>2) New wording: *If unable to bleed on week 4, EOT or post-EOT week 12, the patient should be recalled, as these are critical visits for clinical care.* | Table 3 Trial Assessments and Sample Collection Schedule – Re-treatment |
| Patient Inclusion criteria updated:<br>Previous wording: Infected with HCV genotype 1a or 1b with HCV RNA >LLOQ (lower limit of quantification) on more than one occasion at least six months previously with no intervening results showing undetectable viraemia<br>New wording: *Infected with HCV genotype 1a or 1b with at least one detectable viremia 6 months prior to randomisation (by quantitative HCV RNA, qualitative* | 3.1 Patient Inclusion Criteria |

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| *assay or HCV genotype), with no intervening undetectable results* | |
| Patient Exclusion criteria updated:<br>Previous wording: Previous DAA exposure (previous treatment with pegylated-interferon and/or ribavirin allowed)<br>New wording: *Previous DAA exposure for this infection (previous treatment with pegylated-interferon and/or ribavirin allowed. DAA treatment for a previously cured infection allowed).* | 3.2 Patient Exclusion Criteria |
| The possibility of manual randomisation has been removed | 4.1 Randomisation Practicalities<br>9.1 Method of Randomisation |
| Information on receiving sofosbuvir/ledipasvir at first line has been removed.<br>Previous wording: For patients receiving 8 weeks first line or 12 weeks re-treatment, sofosbuvir/ledipasvir will be dispensed every 4 weeks. For patients randomised to varying first line duration, 4 weeks will be dispensed at the enrolment visit: at the week 4 visit, the precise number of days treatment remaining will be dispensed.<br>New wording: *For patients receiving 12 weeks re-treatment, sofosbuvir/ledipasvir will be dispensed every 4 weeks.* | 5.4.3 Dispensing |
| Information on receiving ombitasvir/paritaprevir/dasabuvir/ritonavir for re-treatment has been removed.<br>Previous wording: or 12 weeks re-treatment | 5.3.3 Dispensing |
| Removal of requirement to submit a follow-up CRF for SAEs.<br>Previous wording: A further SAE Form, indicated as 'Follow-up' should be completed and sent to the MRC CTU at UCL as information becomes available.<br>New wording: *If further information becomes available, updates should be made to the original CRF.* | 7.3.2 Notification Procedure |
| Additional wording to the per-protocol population definition.<br>New wording: *and where the difference between screening and enrolment HCV RNA values would have led to a difference of ≤2 days in allocated duration of DAAs had they been allocated to the varying duration group.* | 9.5 Analysis Plan (Brief) |
| Additional secondary analysis added. | 9.5 Analysis Plan (Brief) |

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| New wording: *A further secondary analysis will exclude reinfections leading to rebound virus, with reinfection determined by genotype and full genome sequencing.* | |
| Protocol version number and date updated on first page and on all page headers. | |
| **Protocol v5.0 28-Apr-2017 approved by REC 08-May-2017 and MHRA 09-May-2017** | |
| **Changes made** | **Sections updated** |
| Duration of varying first-line treatment changed on recommendation of the DMC:<br>Previous wording: 4-6 weeks<br>New wording: 4-7 weeks | Summary of Trial<br>Trial Schema Figure 1<br>Text throughout the entire document |
| Removal of day 42 visit | Table 1 Trial Assessment Schedule – first line treatment real-time tests<br>Table 2 Sample collection schedule – first line treatment sample storage |
| Clarification of when a patient should be recalled for a confirmatory viral load:<br>Previous wording: Therefore any patient with a single HCV RNA >LLOQ after confirmed HCV RNA <LLOQ<br>New wording: *Therefore any patient with a single HCV RNA >LLOQ after 2 consecutive HCV RNA <LLOQ* | 5.2 Definition of Failure on First-Line Treatment and Move to Re-treatment |
| Addition of day 43-49 and changes to HCV VL thresholds | Table 10 Duration of first-line treatment in the intervention biomarker-stratified group |
| Clarification of instructions for missed doses.<br>Previous wording: Patients should be instructed that if vomiting occurs within 6 hours of dosing an additional tablet of trial drug should be taken<br>New wording: *Patients should be instructed that if vomiting occurs within 6 hours of dosing an additional dose of trial drug should be taken* | 5.3.5.E Missed doses<br>5.5.5.E Missed doses |
| **Protocol v6.0 17-Aug-2017 approved by REC 19-Oct-2017 and MHRA 22-Sep-2017** | |
| **Changes made** | **Sections updated** |
| Change of coordinating site address from 22nd September 2017:<br>90 High Holborn,<br>London<br>WC1V 6LJ | Trial Administration |
| Inclusion of genotype 4 patients in the trial, in addition to genotype 1a/1b patients | Throughout the entire document |
| Addition to allow the use of Abbvie 2D | Throughout the entire document |

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| (ombitasvir/paritaprevir/ritonavir) for use against genotype 4. | |
| Addition to allow the use of the Abbvie combination glecaprevir/pibrentasvir for use against genotypes 1a/1b and 4. | Throughout the entire document |
| Removal of wording referring to the 'platform protocol' | Throughout the entire document |
| Removal of the requirement of coagulation markers at follow-up visits | Table 1 Trial Assessment Schedule– first line treatment real-time tests<br>Table 3 Trial Assessments and Sample Collection Schedule – Retreatment |
| Addition of a Pregnancy test at Retreatment EOT+24 visit | Table 3 Trial Assessments and Sample Collection Schedule – Retreatment |
| Existing research expanded to include glecaprevir/pibrentasvir | 1.2 Existing research<br>Table 6 Characteristics of G/P<br>Table 7 Phase 2/3 trials for G/P in non-cirrhotics |
| Patient inclusion criteria updated:<br>Previous wording: 2. Infected with HCV genotype 1a or 1b with at least one detectable viremia 6 months prior to randomisation (by quantitative HCV RNA, qualitative assay or HCV genotype), with no intervening undetectable results<br><br>New wording:<br>2. *Infected with HCV genotype 1a or 1b or 4 with access to first-line treatment appropriate for their genotype (ombitasvir/paritaprevir/(dasabuvir)/ritonavir or glecaprevir/pibrentasvir)*<br>3. *At least one detectable viremia 6 months prior to randomisation (by quantitative HCV RNA, qualitative assay or HCV genotype), with no intervening undetectable results* | 3.1 Patient Inclusion Criteria |
| Clarification of patient exclusion criteria:<br>Previous wording: FEMALES ONLY: Lactating, or pregnant, or planning to become pregnant during the study or within 4 months of the end of the study, or not willing to use effective contraception during the study and for four months after last dose of study medication.<br>New wording: *FEMALES ONLY: Lactating, or pregnant, or planning to become pregnant, or not willing to use effective contraception, during the study and for four months after last dose of study medication.* | 3.2 Patient Exclusion Criteria |

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| Previous wording: MALES only: planning pregnancy with female partner during the study or within 7 months of the end of the study, or not willing to use effective contraception during the study and for seven months after last dose of study medication.<br><br>New wording: *MALES only: planning pregnancy with female partner during the study or within 7 months of the end of the study, or not willing to use effective contraception, during the study and for seven months after last dose of study medication.* | |
| Patient exclusion criteria updated with the addition of G/P excipients:<br><br>New wording: *vitamin E (tocopherol) polyethlyene glycol succinate, sodium stearyl fumarate* | 3.2 Patient Exclusion Criteria |
| Addition of product characteristics for G/P | 5.5 Glecaprevir/pibrentasvir (Maviret®) |
| Clarification that dose changes after initiation of ribavirin should only be made if a participant moves >2.5kg above or below the 75kg weight threshold (ie not for weight fluctuations) | 5.6.3 Dispensing |
| Recommended ARV regimens updated to include a section for regimens compatible with G/P and an additional warning about avoidance of cobicistat during the use of ombitasvir/partaprevir/dasabuvir/ritonavir | 5.12.1 Antiretroviral drugs in HIV-HCV co-infected patients receiving ombitasvir/paritaprevir/dasabuvir/ritonavir or glecaprevir/pibrentasvir<br><br>Table 13 Antiretrovirals which can be administered during STOP-HCV-1 |
| Addition of HBV reactivation for HCV/HBV co-infected participants to the side effects for all DAAs, including those used in this protocol | 7.3.1.D Expectedness |
| Addition of rash as a common toxicity for sofosbuvir and ledipasvir | Table 16 Expected toxicities of sofosbuvir/ledipasvir with or without ribavirin |
| Addition of angioedema as a rare toxicity of ombitasvir/paritaprevir/dasabuvir/ritonavir with or without ribavirin | Table 17 Expected toxicities of ombitasvir/partaprevir /dasabuvir/ritonavir |
| Table added describing G/P side-effects by frequency | Table 18 Expected toxicities of glecaprevir/pibrentasvir |
| Additional subgroup analyses added:<br><br>New wording:<br>• Duration strategy (protocol v4.0 or earlier vs protocol v5.0 or later)<br>• First-line treatment regimen | 9.5.1 Planned subgroup analyses |

| **Protocol v7.0** | |
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| **Changes made** | **Sections updated** |
| Removal of coordinating site address prior to the 22nd September 2017. | Trial Administration |
| The trial design has been amended to a *partial* factorial design:<br><br>Participants randomised to 8 weeks glecaprevir/pibrentasvir will not receive ribavirin. | Summary of Trial<br><br>Throughout entire document |
| Additional wording in Study Hypotheses:<br><br>New wording:<br>*(iv)* Adjunctive ribavirin improves cure rates with biomarker-stratified short-course and fixed duration DAA first-line regimens *that are shorter than the full licensed duration of therapy.* | Summary of Trial |
| Additional information on randomisation:<br><br>New wording:<br>• adjunctive ribavirin or not *(this randomisation will be a partial factorial in those receiving a shorter course than the full licensed duration of therapy).* | Summary of Trial |
| Additional information on the ribavirin randomisation:<br><br>New wording: *Note: as above, the ribavirin randomisation will be a partial factorial in those receiving a shorter course than the full licensed duration of therapy.* | Trial Schema |
| Additional wording on shortened durations of therapy:<br><br>New wording: *There are two important questions: first, is it possible to identify patients who will cure with shorter course treatments? And second, is it more effective, and cost-effective, to try to cure as many patients as possible with a shorter-duration of initial therapy, accepting that a proportion who do not cure initially will need re-treatment, on which they may or may not achieve cure?* | 1.3 Shortened Durations of Therapy |
| Additional wording on the study rationale:<br><br>New wording: The trial will therefore also test whether the addition of ribavirin is beneficial in short course treatment, using a *partial* factorial design *in those receiving shorter than the full licensed duration of therapy. Specifically:*<br><br>*Ombitasvir/paritaprevir/ritonavir with or without dasabuvir*<br>*All participants randomised to varying duration DAA treatment with this DAA combination will be additionally* | 1.4 Rationale for Study |

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| *factorially randomised to adjunctive ribavirin or not. The rationale for the factorial randomisation in both groups (fixed and varying duration) is that the '8 week' treatment arm still represents a shorter arm than standard-of-care.*<br><br>*Glecaprevir/pibrentasvir*<br>*All participants randomised to varying duration DAA treatment with this DAA combination will be additionally factorially randomised to adjunctive ribavirin or not. However, participants randomised to the 8 week treatment group will not be additionally randomised to adjunctive ribavirin or not, since 8 weeks of this combination without ribavirin is the licenced, standard-of-care indication for mild HCV.* | |
| Addition to randomisation design:<br><br>New wording:<br>▪ open-label adjunctive ribavirin or not (1:1) *(not those receiving glecaprevir/pibrentasvir and randomised to fixed 8 weeks first-line treatment)* | 4. Registration & Randomisation<br><br>5.1 Introduction |
| Clarification on which visits the Ribavirin dosing should be checked:<br><br>New wording: If a patient previously weighing >75 kg has lost weight and falls to more than 2.5kg below the 75 kg body-weight threshold at the *day 28 visit on first-line or at the re-treatment week 4 or week 8 visits, then* ribavirin dose adjustment should be undertaken as above. | 5.6.3 Dispensing |
| Additional clarification on the primary endpoint:<br><br>New wording: *The primary endpoint of the trial is the overall cure rate after first-line and re-treatment, specifically to address the question as to whether failing on a shorter duration treatment ultimately affects overall chance of cure, or whether the percentages cured with shorter treatment can make it more cost-effective to give everyone shorter courses initially, and then retreat those who do not achieve cure. The specific first-line cure rates are not critical to answering either of these questions.* | 5.7.2 Choice of 8 week first-line fixed duration control group |
| Clarification for pharmacies on conducting drug inventories:<br><br>Previous wording: and logs returned to MRC CTU at UCL.<br><br>New wording: *It is recommended that* inventories be conducted monthly. | 5.9 Accountability & Unused Drugs |
| Clarification on which website source should be used for assessing adverse events:<br><br>Previous wording: International GSI Grading Scale for | 6.3 Procedures for assessing safety<br><br>7.3.1.B Severity or grading of adverse |

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| Severity of Adverse Events and Laboratory Abnormalities<br><br>New wording: *Division of AIDS table for grading the severity of adult and paediatric adverse events.* | events |
| New safety warning added for ombitasvir/paritaprevir/(dasabuvir)/ritonavir:<br><br>*Depression*<br>▪ *Cases of depression and more rarely of suicidal ideation and suicide attempt have been reported with ombitasvir/paritaprevir/(dasbuvir) ritonavir treatment in combination with ribavirin in the majority of the cases. While psychiatric problems including depression are well described with ribavirin (Table 19) and although some patients had a previous history of depression, psychiatric illness and/or substance abuse, a causal relation with ombitasvir/paritaprevir/(dasbuvir) ritonavir could not be excluded.* | |
| Additional information on the statistical considerations of the randomisation method:<br><br>New wording: *The randomisation will be implemented as a pure factorial, that is individuals randomly assigned to any one of four groups (fixed vs varying; adjunctive ribavirin or not). To accommodate the partial factorial, those receiving glecaprevir/pibrentasvir will be considered randomised to 8 weeks treatment without ribavirin (i.e. the ribavirin randomisation will be ignored in these groups). This preserves the 1:1 randomisation to fixed:varying duration overall.* | 9.1 Method of Randomisation |
| Additional wording on the sample size:<br><br>New wording: (in particular first-line cure rates might be expected to be higher with 8 weeks glecaprevir/pibrentasvir since this is the licenced indication, albeit without much real-world experience to date)<br><br>New wording: *The sample size for the fixed vs duration non-inferiority comparison is conducted under the null hypothesis for the ribavirin superiority comparison (i.e. no effect). Given its partial factorial nature, estimates of the effect of adjunctive ribavirin will be determined from generalised linear models which include terms to reflect the randomisations and the specific first-line DAA regimen received, so that patients randomised to 8 weeks' glecaprevir/pibrentasvir effectively do not contribute to this comparison. We estimate that this will be approximately 25% of patients (102). 306 patients* | 9.3 Sample size |

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| *randomised to adjunctive ribavirin or not provides 75-85%* power to identify a 10% improvement in first-line cure rate associated with adjunctive ribavirin *for first-line cure rates 83-86% without and 93-96% with ribavirin (two-sided alpha=0.05) and >80% power to identify a 15% improvement in first-line cure rate associated with adjunctive ribavirin for first-line cure rates 60-80%,* allowing for 5% early withdrawal as above (primary outcomes will be imputed). | |
| Updated information on the analysis plan:<br><br>Previous wording: Risk differences between groups, and their 95% CI, would be estimated using Poisson regression.<br><br>New wording: Risk differences between groups, and their 95% CI, would be estimated using *binomial* regression *on the risk difference scale using a generalised linear model as that is the scale on which the non-inferiority margin is pre-specified. However, in case of non-convergence due to closeness to the boundary (cure probability equalling 1) the risk ratio scale will also be considered.*<br><br>New wording: *Secondary analyses will use Bayesian methods to directly estimate the probability that each intervention regimen is 1%, 2%, 3%, 4% etc worse than control.*<br><br>New wording: Primary analyses of outcomes restricted to first-line therapy will stratify by the first-line DAA duration received (protocol v4.0 or earlier vs protocol v5.0 or later) and by first-line regimen *by including these terms as main effects, together with randomised group (with and without interactions between randomised group).* | 9.5 Analysis Plan (Brief) |
| Changes to the participant reimbursement:<br><br>Previous wording: (up to £10)<br><br>New wording: payment to cover their travel costs *and time* for three research visits in the initial treatment phase *(£50 per visit)* and any retreatment visits *(£25 per visit).* | 10.2.1 Ethical Considerations |

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