Simplified Monitoring - A Randomised Trial in hepatitis C

A phase IIIb, open-label, multicentre, international randomised controlled trial of simplified treatment monitoring for 8 weeks glecaprevir (300mg)/pibrentasvir (120mg) in chronic HCV treatment naïve patients without cirrhosis

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Protocol Synopsis

Title	**SMART-C** A phase IIIb, open-label, multicentre, international randomised controlled trial of simplified treatment monitoring for 8 weeks glecaprevir (300mg)/pibrentasvir (120mg) in chronic HCV treatment naïve patients without cirrhosis
Protocol registration no.	ClinicalTrials.gov Identifier: NCT03117569
Background and rationale	The capacity to scale-up interferon-free DAA therapy would be enhanced by simplified treatment monitoring strategies. The "next generation" DAA regimen of glecaprevir (300mg)/pibrentasvir (120mg), a protease inhibitor and NS5A inhibitor, provides key features for HCV treatment simplification, including on-treatment monitoring: 1) pangenotypic activity with extremely high efficacy (SVR>95%); 2) no relationship between time to undetectable HCV RNA and SVR; 3) minimal drug-related toxicity; 4) ease of dosing (three pills once daily); and short duration (8 weeks in non-cirrhosis and 12 weeks in cirrhosis for treatment naïve patients).[1,2] In phase II and III clinical trials in participants without cirrhosis, 8 weeks of glecaprevir (300mg)/pibrentasvir (120mg) has provided intention-to-treat SVR rates of 99.1%, 98%, 97%, and 93.1% in genotype 1, 2, 3, and 4-6 populations, respectively.[9,10,11] Current standard on-treatment monitoring in clinical trials involves clinic-based visits every 4 weeks. In the DAA era where treatments are highly tolerable, effective and short duration, this intensive monitoring strategy may no longer be required. A simplified on-treatment monitoring strategy is hypothesised to be non-inferior to the standard clinical trial on treatment monitoring strategy. If successful, a simplified on-treatment monitoring strategy is likely to be highly attractive to patients, clinicians and health care payers. It has the potential to improve the rapid scale up of treatment providing population level benefits in the reduction of global hepatitis C disease burden.
Hypothesis	In treatment naïve non-cirrhosis patients with chronic HCV (genotypes 1-6) the sustained virological response rate 12 weeks following treatment with glecaprevir (300mg)/pibrentasvir (120mg) among those receiving a

	simplified monitoring schedule will be non-inferior to that in those receiving a standard monitoring schedule based on the intention-to-treat (ITT) population.
Study objectives	**Primary Objective:** To compare the proportion of participants with undetectable HCV RNA (HCV RNA <LLOQ) at 12 weeks post-treatment (SVR12) following 8 weeks treatment with glecaprevir (300mg)/pibrentasvir (120mg) in HCV treatment naïve non-cirrhosis chronic HCV patients who have received a standard versus simplified schedule of safety and virological monitoring (ITT analysis). **Secondary Objectives:** • To compare the proportion of participants achieving SVR12 between those who received a standard versus simplified schedule of safety and virological monitoring based on mITT population; • To evaluate the proportion adherent to treatment and study visits (both on-treatment adherence and early treatment discontinuation); • To evaluate patient reported outcomes following treatment; • To evaluate safety and tolerability by monitoring adverse events during treatment; • To measure patient satisfaction on both arms; • To evaluate the prevalence and impact of baseline Resistance Associated Substitutions (RAS) on SVR12; • To evaluate cost-effectiveness of simplified monitoring; • To evaluate immunovirological factors associated with treatment clearance. **Exploratory Objective:** • To measure the provider acceptability of the simplified monitoring strategy.
Participant population	A total of 375 participants with chronic HCV will be enrolled. **Inclusion criteria** Participants must meet all of the following inclusion criteria to be eligible to participate in this study. 1) Have voluntarily signed the informed consent form.

	2) 18 years of age or older. 3) Chronic HCV infection as defined by anti-HCV antibody or HCV RNA detection for greater than 6 months. 4) HCV RNA plasma ≥ 10,000 IU/ml at screening. 5) HCV genotype 1-6. 6) HCV treatment naïve (no prior treatment with an approved or investigation anti-HCV medication). 7) Stage F0-3, based on: hepatic elastography <12.5 kPa on Fibroscan® or APRI <1.0. 8) If co-infection with HIV is documented, the subject must meet the following criteria: - ART naïve with CD4 T cell count >500 cells/mm^3; OR - On a stable ART regimen (containing only permissible ART – see section 3.2) for >8 weeks prior to screening visit, with CD4 T cell count >200 cells/mm^3 and a plasma HIV RNA level below the limit of detection. 9) Negative pregnancy test at screening and baseline (females of childbearing potential only). 10) All fertile females must be using effective contraception during treatment and during the 30 days after treatment end. **Exclusion criteria** Participants who meet any of the exclusion criteria are not to be enrolled in this study. 1) History of any of the following: a. Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with the participant treatment, assessment or compliance with the protocol; participants currently under evaluation for a potentially clinically significant illness (other than HCV) are also excluded. b. Clinical hepatic decompensation (i.e. ascites, encephalopathy or variceal haemorrhage).

	c. Solid organ transplant. d. History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs. 2) Any of the following lab parameters at screening: a. ALT > 10 x ULN b. AST > 10 x ULN c. Direct bilirubin > ULN d. Platelets < 90,000/µL (cells/mm^3) if Fibroscan® <12.5 kPa OR < 150,000/µL (cells/mm^3) if Fibroscan® is unavailable and patient is included with APRI <1 e. Creatinine clearance (CL_{cr}) < 50 mL/min f. Haemoglobin < 12g/dL for males; <11g/dL for females g. Albumin < LLN h. INR > 1.5 ULN unless subject has known haemophilia or is stable on an anticoagulant regimen affecting INR 3) Pregnant or breastfeeding female. 4) HBV infection (HBsAg positive). 5) Use of prohibited concomitant medications as described in section 5.3. 6) Chronic use of systemically administered immunosuppressive agents (e.g. prednisone equivalent > 10 mg/day for >2 weeks). 7) Therapy with any anti-neoplastic or immunomodulatory treatment (including supraphysiologic doses of steroids and radiation) ≤6 months prior to the first dose of study drug. 8) Any investigational drug ≤6 weeks prior to the first dose of study drug. 9) Ongoing severe psychiatric disease as judged by the treating physician. 10) Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, propoxyphene, or alcohol, with the exception of a positive result (including methadone) associated with documented short-term use or chronic stable use of a prescribed medication in that class. 11) Injecting drug use within the previous six months. 12) Inability or unwillingness to provide informed consent or abide by the

	requirements of the study.
Study design	This study will be conducted as a Phase IIIb, randomised, controlled, multicentre, international trial. There will be a maximum screening period of 6 weeks prior to Baseline. Eligible patients will be randomised into one of two on-treatment monitoring strategies; standard clinical trial monitoring (4-weekly on-treatment visits) vs simplified monitoring (no on-treatment visits). Randomisation will be 1:2 (standard vs simplified) and all participants will receive treatment with glecaprevir (300mg)/pibrentasvir (120mg) for 8 weeks. All participants will attend the clinic for screening and baseline visit. Randomisation will occur at the baseline visit. The two on-treatment monitoring strategies will differ as follows: • ***Standard monitoring arm participants*** will have on-treatment clinic visits at weeks 4 and 8 (EoT). • ***Simplified monitoring arm participants*** will have no on-treatment clinic visits. Study nurse phone contact will also be made to participants in BOTH arms 1-2 days prior Week 4 and EoT (Week 8) visits to provide standardized reporting of adverse events, concomitant medication and adherence. One post treatment clinic visit will be conducted at SVR12 (week 20) for all participants.
Treatment of participants	Participants will receive 8 weeks of glecaprevir (300mg)/pibrentasvir (120mg) as a co-formulated three tablets daily regimen. Dose modifications are prohibited.
Study procedures	Refer to the Study Schedule of Assessments.
Statistics	**Sample Size** Assuming an SVR12 of 96% in both arms a sample size of 375 provides >80% power to detect non-inferiority at a 6% level. **Assessments of efficacy** ***Primary endpoints:*** 1. SVR12 defined as the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment (week 20) based on ITT population.

	Secondary endpoints: 2. SVR12 defined as the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment (week 20) based on mITT population. 3. Proportion adherent to treatment and study visits (on-treatment adherence and early treatment discontinuation); 4. Change in health-related quality of life during treatment (measured by EQ-5D-3L); 5. Resistance associated substitutions (RAS): SVR12 in participants with and without baseline RAS, and RAS distribution in participants with virological failures; 6. Patient treatment satisfaction measured by a questionnaire applied to all participants; **Assessments of safety** ***Safety endpoints:*** 7. Proportion of patients with common adverse events (reported in greater than 5%). 8. Proportion of patients with at least one severe or potentially life threatening (grade 3 or 4) adverse event. 9. Proportion of patients with un-scheduled clinic visits. **Exploratory endpoint** 10. Provider acceptability of simplified monitoring strategy.

Schedule of Assessments (Standard monitoring arm)

Assessment / Procedure	**Screening**	**Baseline**	**On-treatment Phase**		**Follow-Up Phase**
Study weeks	**-6 to 0**	**0**	**4**	**8 (EoT)**	**20 (SVR12)**
Study Days	**-42 to 0**	**0**	**28**	**56**	**140**
Visit Window (Days)			***+/- 3***	***+/- 3***	***+/- 14***
Informed consent	x				
Medical history / Patient demographics	x				
Randomisation		x			
Dispense study drug		x	x		
Return study drug					x
Vital signs & physical measurements	x	x	x	x	x
HCV-RNA testing (Local Laboratory)	x			x	x
HCV genotyping (Local Laboratory)	x[a]				
Study Drug Adherence Survey			x[b]	x[b]	
Health outcomes survey (EQ-5D-3L)	x				x
Participant Satisfaction Survey	x				x
Fibroscan® / APRI	x[c]				
Liver function tests/ Full blood count/ Biochemistry	x	x	x	x	x
Clotting (INR)	x				
Urinary Drug Screen	x				
HIV & HBV serology	x				
Pregnancy Test[d]	x	x	x	x	x
Adverse events		x	x[b]	x[b]	x
Concomitant medication	x	x	x[b]	x[b]	x
Research Specimen Collection					
EDTA Whole Blood (4mL)	x				
EDTA plasma (10mL)	x[e]	x[e]	x	x	x
PBMCs[f] (60mL)	x		x		x

[a]Within 5 years prior to screening; [b]Completed by study nurses during phone contact; [c]Fibroscan within 6 months prior to screening; [d]Women of child bearing potential only; [e]20mL at Screening and Baseline; [f]At selected sub-study sites only

Schedule of Assessments (Simplified monitoring arm)

Assessment / Procedure	**Screening**	**Baseline**	**On-treatment Phase**		**Follow-Up Phase**
Study weeks	**-6 to 0**	**0**	**4**	**8 (EoT)**	**20 (SVR12)**
Study Days	**-42 to 0**	**0**	**28**	**56**	**140**
Visit Window (Days)			***+/- 3***	***+/- 3***	***+/- 14***
Informed consent	x				
Medical history / Patient demographics	x				
Randomisation		x			
Dispense study drug (8 weeks)		x			
Return study drug					x
Vital signs & physical measurements	x	x			x
HCV-RNA testing (Local Laboratory)	x				x
HCV genotyping (Local Laboratory)	x[a]				
Study Drug Adherence Survey			x[b]	x[b]	
Health outcomes survey (EQ-5D-3L)	x				x
Participant Satisfaction Survey	x				x
Fibroscan® / APRI	x[c]				
Liver function tests/ Full blood count/ Biochemistry	x	x			x
Clotting (INR)	x				
Urinary Drug Screen	x				
HIV & HBV serology	x				
Pregnancy Test[e]	x	x	x[d]	x[d]	x
Adverse events		x	x[b]	x[b]	x
Concomitant medication	x	x	x[b]	x[b]	x
Research Specimen Collection					
EDTA Whole Blood (4mL)	x				
EDTA plasma (10mL)	x[f]	x[f]			x
PBMCs[g] (60mL)	x				x

[a]Within 12 months prior to screening; [b]Completed by study nurse during phone contact; [c]Fibroscan within 6 months prior to screening; [d]Self-completed by participants at home; [e]Women of child bearing potential only; [f]20mL at Screening and Baseline; [g]At selected sub-study sites only

1.0 Background and rationale

Chronic hepatitis C virus (HCV) treatment was interferon-based for two decades, with the addition of ribavirin (RBV),[3] Pegylated interferon (PEG-IFN),[4] and initial protease inhibitor direct acting antiviral (DAA) therapies (telaprevir, boceprevir)[5,6] providing stepwise improvements in the rate of sustained virological response (SVR). Despite these improvements in interferon-containing regimens, treatment uptake remained low in most countries, ranging from <1% to a maximum of 5% of people with chronic HCV initiating therapy each year.[7]

Fortunately, recent years have seen a revolution in HCV therapeutic development, in particular the interferon-free direct acting antiviral (DAA) regimens.[8] Short, simple (once daily dosing oral regimens), highly tolerable, short-duration (8-12 weeks) therapy with pangenotypic potency and extremely high efficacy (cure rates above 95%) will soon be the norm. The broad implementation of such therapeutic regimens has the potential to produce one of the major turnarounds in disease burden seen in public health and clinical medicine.

The capacity to scale-up interferon-free DAA therapy would be enhanced by simplified treatment monitoring strategies. The "next generation" DAA regimen of glecaprevir (300mg)/pibrentasvir (120mg), a protease inhibitor and NS5A inhibitor, provides key features for HCV treatment simplification, including on-treatment monitoring: 1) pangenotypic activity with extremely high efficacy (SVR>95%); 2) no relationship between time to undetectable HCV RNA and SVR; 3) minimal drug-related toxicity; 4) ease of dosing (three pills once daily); and short duration (8 weeks in non-cirrhosis and 12 weeks in cirrhosis for treatment naïve patients).[1,2] In phase II and III clinical trials in patients without cirrhosis, 8 weeks of glecaprevir (300mg)/pibrentasvir (120mg) has provided intention-to treat SVR rates of 99.1%, 98%, 97%, and 93.1% in genotype 1, 2, 3, and 4-6 populations, respectively with extremely low rates of drug-related toxicity.[9,10,11]

Current standard on-treatment monitoring in clinical trials involves clinic-based visits every 4 weeks. In the DAA era where treatments are highly tolerable, effective and short duration, this intensive monitoring strategy may no longer be required. A simplified on-treatment monitoring strategy is hypothesised to be non-inferior to the standard clinical trial on treatment monitoring strategy. If successful, a simplified on-treatment monitoring strategy is likely to be highly attractive to patients, clinicians and health care payers. It has the potential to improve the rapid scale up of treatment providing population level benefits in the reduction of global hepatitis C disease burden.

2.0 Study objectives

2.1 Hypothesis

In treatment naïve non-cirrhosis patients with chronic HCV (genotypes 1-6) the sustained virological response rate 12 weeks following treatment with glecaprevir (300mg)/pibrentasvir (120mg) among those receiving a simplified monitoring schedule will be non-inferior to that in those receiving a standard monitoring schedule based on the intention-to-treat (ITT) population.

2.2 Primary objective

To compare the proportion of patients with undetectable HCV RNA (HCV RNA <LLOQ) at 12 weeks post-treatment (SVR12) following 8 weeks treatment with glecaprevir (300mg)/pibrentasvir (120mg) in HCV treatment naïve non-cirrhosis chronic HCV patients who have received a standard versus simplified schedule of safety and virological monitoring.

2.3 Secondary objective(s)

- To compare the proportion of participants achieving SVR12 between those who received a standard versus simplified schedule of safety and virological monitoring based on mITT population;
- To evaluate the proportion adherent to treatment and study visits (both on-treatment adherence and early treatment discontinuation);
- To evaluate patient reported outcomes following treatment;
- To evaluate safety and tolerability by monitoring adverse events during treatment;
- Patient treatment satisfaction measured by a questionnaire applied to all participants;
- To evaluate the prevalence and impact of baseline Resistance Associated Substitutions (RAS) on SVR12;
- To evaluate cost-effectiveness of simplified monitoring;
- To evaluate immunovirological factors associated with treatment clearance.

2.4 Exploratory objective

- To measure the provider acceptability of the simplified monitoring strategy.

3.0 Participant population

3.1 Number of Participants and Participant Selection

375 participants will be enrolled through INPACT-C network sites in Australia, New Zealand, North

America (United States and Canada) and Europe. The Kirby Institute may close or suspend screening at specific sites prior at to reaching 375 participants in order to manage the total study enrolment numbers.

3.2 Inclusion criteria

Participants must meet all of the following inclusion criteria to be eligible to participate in this study.

1) Have voluntarily signed the informed consent form.
2) 18 years of age or older.
3) Chronic HCV infection as defined by anti-HCV antibody or HCV RNA detection for greater than 6 months.
4) HCV RNA plasma ≥ 10,000 IU/ml at screening.
5) HCV genotype 1-6.
6) HCV treatment naïve (no prior treatment with an approved or investigation anti-HCV medication).
7) Stage F0-3, based on hepatic elastography <12.5 kPa on Fibroscan® or APRI <1.0.
8) If co-infection with HIV is documented, the subject must meet the following criteria:
   - ART naïve with CD4 T cell count >500 cells/mm^3;

     OR

   - On a stable ART regimen for >8 weeks prior to screening visit, with CD4 T cell count >200 cells/mm^3 and a plasma HIV RNA level below the limit of detection.

   Permissible ARTs include:

   - Raltegravir
   - Dolutegravir
   - Rilpivirine
   - Elvitegravir/cobicistat
   - Tenofovir disoproxil fumarate
   - Tenofovir alafenamide
   - Emtricitabine
   - Lamivudine
   - Abacavir
9) Negative pregnancy test at screening and baseline (females of childbearing potential only).

10) All fertile females must be using effective contraception during treatment and during the 30 days after treatment end.

3.3 Exclusion criteria

Participants who meet any of the exclusion criteria are not to be enrolled in this study.

1) History of any of the following:
    a. Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with the participant treatment, assessment or compliance with the protocol; participants currently under evaluation for a potentially clinically significant illness (other than HCV) are also excluded.
    b. Clinical hepatic decompensation (i.e. ascites, encephalopathy or variceal haemorrhage).
    c. Solid organ transplant.
    d. History of severe, life-threatening or other significant sensitivity to any excipients of the study drugs.
2) Any of the following lab parameters at screening:
    a. ALT > 10 x ULN
    b. AST > 10 x ULN
    c. Direct bilirubin > ULN
    d. Platelets < 90,000/µL (cells/mm^3) if Fibroscan® <12.5 kPa OR < 150,000/µL (cells/mm^3) if Fibroscan® is unavailable and patient is included with APRI <1
    e. Creatinine clearance (CL_{cr}) < 50 mL/min
    f. Haemoglobin < 12g/dL for males; <11g/dL for females
    g. Albumin < LLN
    h. INR > 1.5 ULN unless subject has known haemophilia or is stable on an anticoagulant regimen affecting INR
3) Pregnant or breastfeeding female.
4) HBV infection (HBsAg positive).
5) Use of prohibited concomitant medications as described in section 5.3.
6) Chronic use of systemically administered immunosuppressive agents (e.g. prednisone equivalent > 10 mg/day for >2 weeks).
7) Therapy with any anti-neoplastic or immunomodulatory treatment (including supraphysiologic doses of steroids and radiation) ≤6 months prior to the first dose of study drug.
8) Any investigational drug ≤6 weeks prior to the first dose of study drug.
9) Ongoing severe psychiatric disease as judged by the treating physician.

10) Positive result of a urine drug screen at the Screening Visit for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, propoxyphene, or alcohol, with the exception of a positive result (including methadone) associated with documented short-term use or chronic stable use of a prescribed medication in that class.
11) Injecting drug use within the previous six months.
12) Inability or unwillingness to provide informed consent or abide by the requirements of the study.

4.0 Study design

4.1 Summary of study design

This study will be conducted as a Phase IIIb, randomised, controlled, multicentre, international trial.

There will be a maximum screening period of 6 weeks prior to Baseline. Eligible patients will be randomised into one of two on-treatment monitoring strategies; standard clinical trial monitoring (4-weekly on-treatment visits) vs simplified monitoring (no on-treatment visits) (see Figure 1). Randomisation will be 1:2 (standard vs simplified) and all participants will receive treatment with glecaprevir (300mg)/pibrentasvir (120mg) for 8 weeks.

All participants will attend the clinic for screening and baseline visit. Randomisation will occur at the baseline visit.

The two on-treatment monitoring strategies will differ as follows:

- ***Standard monitoring arm participants*** will have on-treatment clinic visits at weeks 4 and 8 (EoT).
- ***Simplified monitoring arm participants*** will have no on-treatment clinic visits.

Study nurse phone contact will also be made to participants in BOTH arms 1-2 days prior Week 4 and EoT (Week 8) visits to provide standardized reporting of adverse events, concomitant medication and adherence.

One post treatment clinic visit will be conducted at SVR12 (week 20) for all participants.

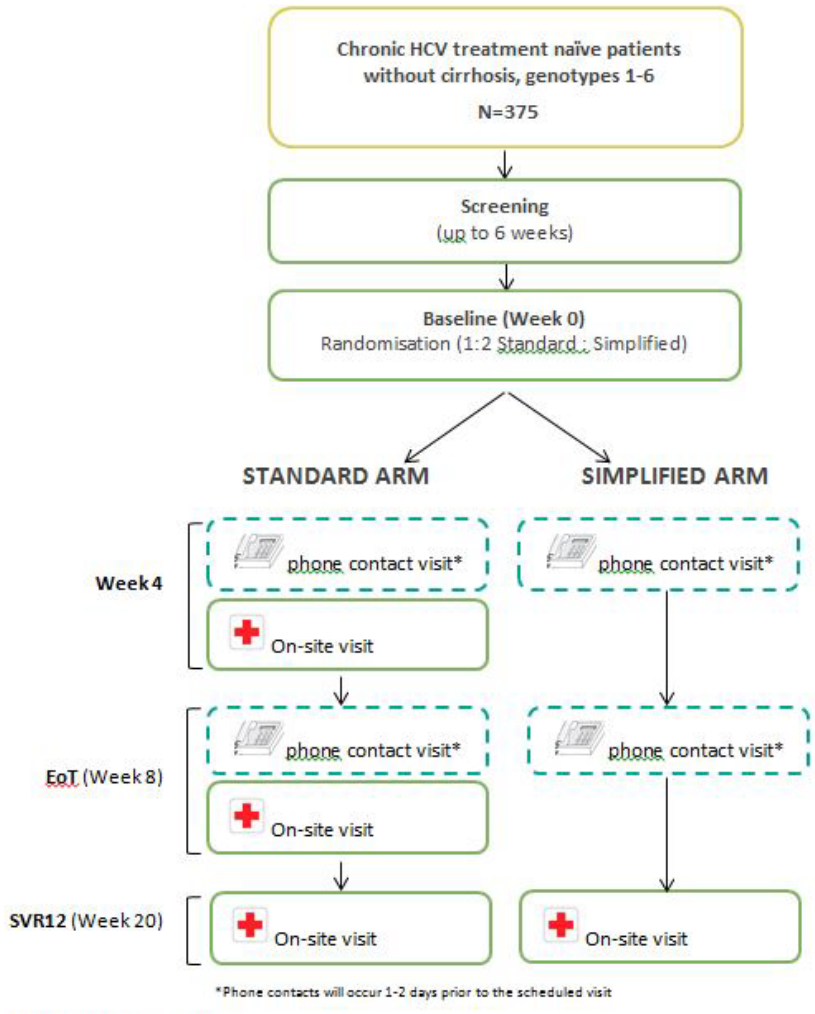

Figure 1: Study schema

4.2 Visit Schedule

All participants will complete screening, on-treatment and post-treatment assessments as outlined in the Schedule of Assessments and described in Section 6.0.

Screening assessments must be completed within 6 weeks prior to Baseline.

Following Screening and Baseline:

- ***Standard monitoring arm participants*** will have on-treatment clinic visits at weeks 4 and EoT (week 8). Post treatment visit will be conducted at SVR12 (week 20).
- ***Simplified monitoring arm participants*** will have no on-treatment clinic visits. One post treatment visit will be conducted at SVR12 (week 20).

All participants will have study nurse phone contact-based visits at week 4 and EoT (week 8). During phone contact visits the following will be completed: adherence survey, adverse events and concomitant

medications. The phone contact visits for participants in both arms will be undertaken 1-2 days prior to their scheduled visits.

4.3 Treatment Discontinuation Criteria

Study drug may be discontinued for reasons including, but not limited to, the following:

- AEs or laboratory abnormalities for which study drug discontinuation is deemed necessary by the Investigator and/or the Medical Monitor
- Significant protocol violation.
- Participant request to discontinue study drug or withdraw from the study for any reason.
- Discontinuation of the study by the Kirby Institute, regulatory agencies or a Human Research Ethics Committee / Research Ethics Committee / Institutional Review Board.

In the event that a positive pregnancy test result is obtained in a female participant during treatment with glecaprevir/pibrentasvir, the administration of study drug may be continued at the Principal Investigator's discretion after discussion with the participant, if the benefit of continuing study drug is felt to outweigh the potential risk.

Participants who cease study medication will, wherever possible, continue to be followed up according to the protocol study plan by completing the EoT visit at the time of treatment termination and SVR12 visit at week 20. Participants may revoke consent for follow-up without jeopardizing their relationship with either their doctor or the UNSW. If a participant wishes to withdraw from the study then, if possible, all assessments scheduled for the SVR12 (week 20) visit should be completed.

5.0 Treatment of participants

Participants will receive eight week of open-label glecaprevir (300mg)/pibrentasvir (120mg) in an oral once-daily fixed dose. Dose modifications are prohibited.

5.1 Method of Assigning Participants to Treatment Groups (Randomisation)

At the Screening Visit, all participants will be assigned a screening ID.

For participants who meet the study selection criteria and are enrolled in the study, the site personnel will assign a Participant ID number which will then be retained by the participant for the duration of the study. The site personnel will randomise the participant to one of the two treatment groups at baseline via the study randomisation system.

Randomisation will be 1:2 (standard:simplified). Randomisation will be using blocks and will be stratified by country and genotype (1 vs non-1).

5.2 Study Drug and Study Visit Adherence

Treatment will be administered in four-weekly supply for standard arm participants and eight-weekly supply for simplified arm participants.

All participants will be required to return the study drug to the site at the SVR12 visit. Participants in the standard arm will be instructed to only return all study medication at SVR12 to provide standardised drug accountability assessments across the two arms.

Treatment adherence will be also recorded through an adherence questionnaire completed at Week 4 and EoT via the phone-contact visits as described in section 6.2. Study visit adherence will be recorded in the eCRF.

5.3 Prior and Concomitant Medications

Concomitant medication must be recorded in the source documents and eCRF from screening until the SVR12 visit.

Subjects must be able to safely discontinue any prohibited medications or supplements listed in 1 at least 14 days or 10 half-lives (whichever is longer) prior to the first dose of glecaprevir/pibrentasvir and not use these during the entire Treatment Period and for 14 days following discontinuation of study drugs.

Table 1. Contraindicated and non-recommended concomitant medications with glecaprevir/pibrentasvir

Drug Class	Drug(s) within Class that are contraindicated/not recommended	Clinical Comments
Antiarrhythmics	Digoxin	Digoxin dose should be reduced by 50% when coadministered with glecaprevir/pibrentasvir.
Anticoagulants	Dabigatran etexilate	Use of glecaprevir/pibrentasvir may increase dabigatran exposure, therefore concomitant use is not recommended.
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital	May decrease DAA exposure leading to a potential loss of therapeutic activity, therefore not recommended.
Antihistamine	Astemizole Terfenadine	Exposures to Astemizole and Terfenadine may be increased, therefore not recommended.
Antimycobacterial	Rifampin Rifabutin	May decrease DAA exposure leading to a potential loss of therapeutic activity, therefore not recommended.
Ethinyl estradiol-containing products	Ethinyl estradiol-containing medications (such as combined oral contraceptives and hormone replacement therapy)	Potential for ALT elevations, therefore not recommended.
Gastrointestinal pro-kinetic agent	Cisapride	It is a CY3PA4 substrate. Concomitant use is not recommended.
Herbal Product	All herbal supplements (including milk thistle) St. John's Wort *(Hypericum perforatum)* Red yeast rice (monacolin K)	May decrease DAA exposure leading to a potential loss of therapeutic activity, therefore not recommended.
HIV non-nucleoside reverse transcriptase inhibitor	Efavirenz Etravirine Nevirapine	May decrease DAA exposure leading to a potential loss of therapeutic activity, therefore not recommended.
HIV protease inhibitor	Tipranavir/ritonavir Atazanavir Colbicistat Boosted PIs Darunavir Fosamprenavir Indinavir Lopinavir Ritonavir Saquinavir	May increase DAA exposure, therefore not recommended.
HMG-CoA Reductase Inhibitors *	Atorvastatin Lovastatin Simvastatin Pivastatin	Potential for myopathy including rhabdomyolysis., therefore not recommended.
Chronic systemic immunosuppressants	Corticosteroids (prednisolone equivalent of >10mg/day for >2 weeks) Azathioprine Monoclonal antibodies	
Strong CYP3A inducers	Carbamazepine	

* Some HMG-CoA reductase inhibitors (including atorvastatin, lovastatin, or simvastatin) should not be taken with glecaprevir/pibrentasvir. Participants receiving these statins should either switch to pravastatin or rosuvastatin prior to the first

dose of study drug or interrupt statin therapy throughout the treatment period and until 30 days after the last dose. If switching to or continuing pravastatin or rosuvastatin, it is recommended to reduce the pravastatin dose by 50% or limit the rosuvastatin dose to 10 mg daily while on treatment.

Post-menopausal hormone replacement therapy i.e., estradiol, esterified or conjugated estrogens, as long as they do not contain ethinyl estradiol, may be used with glecaprevir /pibrentasvir at the discretion of the Investigator.

Glecaprevir /pibrentasvir is not recommended for use in patients requiring stable cyclosporine doses > 100 mg per day.

Use of investigational agents or devices for any indication within 2 weeks or 10 half-lives, whichever is longer, prior to study drug administration is contra-indicated.

Should any participant need to initiate treatment with any contra-indicated medication during the study, the Medical Monitor must be consulted prior to the initiation of any contra-indicated medication. In the event that a contra-indicated medication is initiated prior to discussion, the Medical Monitor must be made aware of the use of the contra-indicated medication as soon as possible. Medical Monitor's contact details are listed on the cover of this protocol.

5.4 Methods of contraception:

Women of Childbearing Potential must practice at least one of the following methods of birth control from baseline (or earlier) through at least 30 days after the last dose of study drug (postmenopausal or permanently surgically sterile women are excluded).

- Progestogen-only hormonal contraception (oral, injectable, implantable), initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation (if via hysteroscopy [i.e., Essure], provided that a hysterosalpingogram confirms success of the procedure)
- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Male or female condom with or without spermicide.
- Cap, diaphragm or sponge with spermicide.

- A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier method).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

There are no specific contraception requirements for male participants.

6.0 Study procedures

6.1 Visits and Procedures

The following assessments must be conducted at study visits as per the schedule of assessments:

Vital signs & physical measurements	Sitting systolic and diastolic blood pressure, heart rate, body weight[a], height[a]
FibroScan®	Transient elastography; within 6 months prior to screening. Use APRI in the absence of FibroScan®
Biochemistry	Creatinine, sodium, chloride, potassium and BUN
Liver Function Tests	ALT, AST, GGT, total bilirubin, albumin, alkaline phosphatase, total protein
Full Blood Count	Haemoglobin, haematocrit , White Blood Cells, platelets, neutrophils
Clotting	INR
Urinary Drug Screen	Screen for Opiates (other than methadone and buprenorphrine), Amphetamines and Cocaine
HCV RNA	Must be quantitative at Screening
HCV Genotype	Within 5 years prior to screening
HIV Serology	Anti-HIV Ab
HBV Serology	HBsAg
HCG Pregnancy Test	For women of childbearing potential, a negative urine (or serum) HCG test at screening and baseline
Questionnaires	Adherence survey, EQ-5D-3L, Practitioner Acceptability Questionnaire, Participant Satisfaction Survey

[a] at screening only

The following assessments and procedures must be performed at each visit as specified below:

Screening visit (Week -6 to Week 0) - All participants

- Informed consent
- Medical history and patient demographics
- Concomitant medication

- Vital signs and physical measurements
- Health outcome survey (EQ-5D-3L)
- Participant Satisfaction survey
- Fibroscan®
- HCV RNA and genotype (Local Lab.)
- LFTs, FBC and biochemistry (Local Lab.)
- HIV antibody & HBV serology (Local Lab.)
- Clotting (INR)
- UDS
- Pregnancy test (females of child bearing potential only)
- Research specimen collection (Central Lab.):
    - EDTA plasma & whole blood (at all sites)
    - PBMCs (at selected sub-study sites only)

Baseline visit (Week 0) - All participants

- Vital signs and physical measurements
- LFTs, FBC and biochemistry (Local Lab.)
- Pregnancy test (females of child bearing potential only)
- Adverse Events
- Concomitant medication
- Research specimen collection (Central Lab.): EDTA plasma
- Randomisation
- Study drug dispensed (4-weekly supply for standard arm participants and 8-weekly supply for simplified arm participants)

Week 4 – All participants

Via phone contact 1-2 days prior to week 4. A maximum of three attempts should be made by the site personnel to contact the participant over the phone. Phone contact attempts must be within the visit window allowed per protocol. All attempts must be recorded in the source documents.

- Adverse Events
- Concomitant medication
- Adherence survey

In addition to the above the following assessments will be completed at week 4:

	Standard treatment monitoring group	**Simplified treatment monitoring group**
HOME	Completed at **HOME** by the participant: *NIL*	Completed at **HOME** by the participant: • Pregnancy test (females of child bearing potential only)

CLINIC	Completed at the **CLINIC**:
	• Vital signs and physical measurements
	• LFTs, FBC and biochemistry (Local Lab.)
	• Pregnancy test (females of child bearing potential only)
	• Research specimen collection (Central Lab.):
	  • EDTA plasma (at all sites)
	  • PBMCs (at sub-study sites only)
	• Study drug dispensed (4-weekly supply)
		Completed at the **CLINIC**:
		NIL – participant is not required to attend the clinic

End of Treatment (Week 8) – All participants

Via phone contact 1-2 days prior to week 8. A maximum of three attempts should be made by the site personnel to contact the participant over the phone. Phone contact attempts must be within the visit window allowed per protocol. All attempts must be recorded in the source documents.

- Adverse Events
- Concomitant medication
- Adherence survey

In addition to the above the following assessments will be completed at week 8:

	Standard treatment monitoring group	Simplified treatment monitoring group
HOME	Completed at **HOME** by the participant: *NIL*	Completed at **HOME** by the participant: • Pregnancy test (females of child bearing potential only)
CLINIC	Completed at the **CLINIC**: • Vital signs and physical measurements • HCV RNA (Local Lab.) • LFTs, FBC and biochemistry (Local Lab.) • Pregnancy test (females of child bearing potential only) • Research specimen collection (Central Lab.): • EDTA plasma (at all sites)	Completed at the **CLINIC**: *NIL – participant is not required to attend the clinic*

SVR12 (week 20) - All participants

- Vital signs and physical measurements
- Return study drug
- Health outcome survey (EQ-5D-3L)
- Participant Satisfaction survey
- HCV RNA (Local Lab.)
- LFTs, FBC and biochemistry (Local Lab.)
- Pregnancy test (females of child bearing potential only)
- Adverse Events
- Concomitant medication
- Research specimen collection (Central Lab.):
    - EDTA plasma (at all sites)
    - PBMCs (at selected sub-study sites only)

Unscheduled visits

Unscheduled visits may occur for a number of reasons including, but not limited to, adverse events, early treatment discontinuation or study termination. In the event of treatment or study termination an

unscheduled visit should be performed where possible. In the event of an unscheduled visit the following data may be collected if applicable:

- Adverse Events
- Concomitant medication
- Vital signs and physical measurements
- HCV RNA and genotype (Local Lab.)
- LFTs, FBC and biochemistry (Local Lab.)
- HIV antibody & HBV serology (Local Lab.)
- Pregnancy test (females of child bearing potential only)

6.2 Study Questionnaires

All participants will undertake a number of study questionnaires at selected study visits as described below.

Adherence Survey

Adherence to study drug will be assessed by a structured self-report adherence questionnaire completed at week 4 and EoT (week 8) by the participants with the nurse during the telephone contact visits.

Health Outcomes Survey (EQ-5D-3L)

The EQ-5D-3L health questionnaire provides a simple descriptive profile and a single index value for health status. This information can then be translated into a health utility, which can be used for cost-effectiveness analyses. The EQ-5D-3L will be completed by all participants in the clinic at screening and SVR12 (week 20).

Participant Satisfaction Survey

Participant satisfaction will be assessed via questionnaire completed by all participants at the screening visit and again following the completion to treatment at the SVR12 visit.

Practitioner Acceptability Questionnaire

Acceptability of simplified HCV treatment monitoring will be assessed via study specific questionnaire completed by each site Principal Investigator and the primary Research Nurse prior to the commencement of screening and again following the completion of the SVR12 visit of the last patient at each site.

Practitioner Acceptability Questionnaire will not be completed on a per participant basis. It will only be completed by the practitioners twice during the study: before FPFV and after LPLV.

7.0 Recording and reporting Adverse Events (AEs) and Product Complaints

7.1 Definitions of Adverse Events, Adverse Reactions and Serious Adverse Events

7.1.1 Adverse Event definition

Adverse events and adverse drug reactions may occur in the course of this study and within the specified follow-up period. These events may also occur in screened participants during the screening period prior to enrolment as a result of protocol-specified interventions. Adverse events will be collected for all participants in the clinic at baseline and SVR (week 20) visits and via phone contact at the week 4 and EoT (week 8) visits.

The definition of an adverse event is any untoward medical occurrence in a participant administered with a pharmaceutical product which does not necessarily have a causal relationship with the product.

Pre-existing conditions or diseases that occur during the study (e.g. seasonal allergies, asthma or recurrent headaches) should not be considered as adverse events unless they change in frequency or severity

All adverse events encountered during treatment and for 12 weeks after drug discontinuation must be reported on the Adverse Event Page of the electronic case report form (eCRF).

Laboratory test abnormalities (results outside the normal range) as such should not be reported as adverse events unless they result in a clinically relevant condition including but not limited to modification or discontinuation of study drug. Overdoses of study drug without clinical sequelae should not be reported as an adverse event.

7.1.2 Serious Adverse Event (SAE) (including Serious Adverse Drug Reactions)

The Investigator shall report serious adverse events to the Kirby Institute and AbbVie within twenty-four (24) hours of learning of the event. In addition, the Investigator shall report to the Kirby Institute and AbbVie all pregnancies experienced by a Study subject within 24 hours of learning of the event.

A serious adverse event is defined as any event that results in any of the following:

(i) death;

(ii) a life threatening adverse event experience (i.e., participant was at immediate risk of death from the event as it occurred);

(iii) a persistent or significant disability/incapacity;

(iv) inpatient hospitalisation

(v) prolongation of existing hospitalisation;

(vi) a congenital anomaly/birth defect; or

(vii) an important medical event that jeopardizes the participant and requires medical/surgical intervention to prevent one of the outcomes listed in (i) through (vii) of this definition.

7.2 Assessment of Adverse Events and Serious Adverse Events

7.2.1 Assessment of Causality for Study Drugs and Procedures

The investigator or designee must assess each adverse event for the following:

Relationship

Unlikely:	An adverse event that is unlikely to be related to the use of the drug or procedures.
Possibly:	An adverse event that might be related to the use of the drug or procedures.
Probably:	An adverse event that is likely to be related to the use of the drug or procedures.

7.2.2 Assessment of Severity

The investigator or designee must assess each adverse event for the following:

Severity

Mild:	Discomfort noticed but no disruption of normal daily activity.
Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
Severe:	Incapacitating with inability to work or perform normal daily activity.
Life threatening:	Represents an immediate threat to life.

7.3 Reporting Requirements

7.3.1 Adverse Events

All adverse events from the date of signing the consent form until twelve weeks after the last dose of study drug administration should be reported on the case report form. All clinically significant adverse events should be followed and recorded until its resolution (or stabilization in case it cannot resolve).

Coding

Adverse events will be assigned preferred terms and categorised into system organ classes according to the Medical Dictionary for Drug Regulatory Affairs (MedDRA) classification of the WHO terminology.

7.3.2 Serious Adverse Events

All serious adverse events (SAEs) should be reported within **24 HOURS** of becoming aware of the event to the Kirby Institute and AbbVie by email or fax on the Serious Adverse Event Reporting Form. The appropriate Serious Adverse Event form should be used. Reports should be followed promptly by detailed, written follow-up reports when all information is not included in the initial report. Follow-up reports should be reported within 24 HOURS also. The immediate and follow up reports should identify participants by unique code numbers assigned to study participants rather than personal identification. The investigator must also comply with all applicable ethical and regulatory requirement/s relating to the reporting of serious adverse events.

Any serious adverse event that is ongoing at the post-study follow-up visit must be followed until resolution or until the event stabilizes (for those events that will not resolve).

For deaths, the Principal Investigator will supply the sponsor and the IRB/IEC with any additional requested information (e.g. death certificate, autopsy reports and medical reports).

The Investigator shall make available to both the Kirby Institute and AbbVie promptly such records as may be necessary and pertinent to investigate any adverse event, if specifically requested by AbbVie.

SAE reports must be submitted to **BOTH the Kirby Institute AND AbbVie:**

Kirby Institute: Email: smartc@kirby.unsw.edu.au

Fax: +61 2 9385 9214

AbbVie: Email: PPDINDPharmacovigilance@abbvie.com

7.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Project Team in collaboration with the Medical Officer will review and identify all serious events which fit the criteria of a SUSAR and requiring expedited reporting to relevant parties.

The definition of a SUSAR is a serious adverse event which is both suspected as being related to the drug (i.e. has a reasonable suspected causal relationship and is unexpected) and where the nature and severity is not consistent with known information (e.g. the Investigator's Brochure).

The sponsor must expedite the reporting of all SUSARs to all concerned investigators/institutions, IRB/IEC/s, and regulatory authorities within the reporting timeframe. Reports must comply with the applicable regulatory requirements and ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Researchers must inform the IRB/IEC and regulatory authorities of all SUSARs that occur during the study that may affect the conduct of the study or the safety of the participants or their willingness to continue participation in the study. Researchers must inform the IRB/IEC as soon as possible of any new information from other published or unpublished studies which may have an impact on the continued ethical acceptability of the study or which may indicate the need for amendments to the study protocol.

7.5 Product Complaints

All Product Complaints at any Study Site must be reported to both the Kirby Institute and AbbVie within twenty-four (24) hours.

Kirby Institute: Email: smartc@kirby.unsw.edu.au

Fax: +61 2 9385 9214

AbbVie: Email: RD_PQC_QA@abbvie.com

Product Complaint means any suspected quality defect in the study drug or its package or labelling. Product Complaints may include, but are not limited to:

(i) damaged or broken product or packaging issues;

(ii) product appearance whose color/markings do not match the labeling;

(iii) labeling discrepancies/inadequacies in the labeling/instructions;

(iv) missing components/product.

8.0 Packaging, labelling, storage and accountability of clinical trial supplies

Glecaprevir/pibrentasvir will be provided by AbbVie and should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist.

All participants will be required to return the study drug to the site at the SVR12 visit. Returned study drug must not be dispensed again. Study drug may not be relabeled or reassigned for use by other participants.

A designated person at the study site must receive the study drug shipment. That person must check that the supplies are in good condition and are complete as per the shipping records. Study drugs must be stored in a secure location with limited access. The study drug must only be dispensed according to the protocol and records must be kept detailing supplies received, dispensed to the participant, returned from the participant and returned to the sponsor or destroyed at site, as applicable.

Study staff must not open and count clinical trial supplies prior to dispensing.

8.1 Formulation

Glecaprevir and pibrentasvir are presented as a co-formulated, film-coated, immediate release tablet. The tablet strength is 100 mg glecaprevir and 40 mg pibrentasvir. The tablets are pink-colored, oblong biconvex shaped and debossed with “2nd” on one side.

The tablets do not contain gluten. The tablets contain lactose.

8.2 Packaging and labelling

Glecaprevir/pibrentasvir 100mg/40mg tablets are packaged in bottles of 30 tablets. 3 bottles are required for 4 weeks of treatment, which includes an extra 2 days of treatment. 6 bottles are required for 8 weeks of treatment, which includes an extra 4 days of treatment.

8.3 Storage and handling

Study drug should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied.

Glecaprevir/pibrentasvir should be stored between 15°C (59°F) and 25°C (77°F).

Care should be taken to ensure that the study drug is stored securely away from children and in dry conditions. The study drug should be kept in the original packaging.

8.4 Dosage and administration

The study drug is to be administered orally once a day (three tablets per day) with food. Each participant must be given instructions to maintain approximately the same daily dosing interval between study drug doses. Participants should be instructed to swallow the study drug tablets whole. Participants should be instructed to only remove the tablets from the bottle immediately prior to dosing.

For a missed dose of study drug, participants should be instructed to take the missed dose of study drug as soon as possible during the same day. However, no more than the daily dose of glecaprevir/pibrentasvir should be taken on any calendar day. Participants should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

Participants in the standard arm will be dispensed with four-week supply (three bottles) at the Baseline and Week 4 visits.

Participants in the simplified arm will be dispensed with eight-week supply (6 bottles) at the Baseline visit.

9.0 Biological samples

9.1 Laboratory supplies and sample processing

Laboratory supplies for collection of research specimens (plasma, whole blood and PBMCs) will be supplied by the Kirby Institute.

The following blood samples will be collected as time point specified in the schedule of assessments:

- 10 mL EDTA plasma (20 mL at screening and baseline) for HCV RNA testing, virological factors associated with treatment clearance and future HCV related research;
- 4 mL EDTA whole blood for human genomic DNA analysis;
- 60 mL ACD plasma for PBMCs (sub-study sites only) for immunological factors associated with treatment clearance and future HCV related research;

Samples will be collected by sites and then processed and stored at -80°C (-200°C for PBMCs) at the site local laboratory for bulk shipment to the Kirby Institute laboratory. Detailed sample processing instructions will be provided in the Laboratory Manual.

EDTA plasma samples will be used for study endpoint analysis. HCV viral load will be measured using in-house and commercial assays. Sequencing of the viral genome will also be performed as a more accurate means of genotyping. Data generated from the sequencing may also be used to distinguish relapse from reinfection, to examine the prevalence of mixed infection and to look at factors associated with relapse including RASs.

PBMCs and whole blood samples may be used to examine host factors associated with viral clearance, including but not limited to HLA Type, IL28-B, ISG expression, IP-10 and other biomarkers.

9.2 Shipping of biological samples

Samples must only be shipped to the Kirby Institute laboratory on the instruction from the SMART-C Project Coordinator.

It is the responsibility of each site Principal Investigator to ensure that all site staff handling, packaging, and/or shipping biological samples understand and comply with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods and/or diagnostic specimens.

9.3 Future use of biological samples

After the samples have been analyzed for the study endpoints as specified in the protocol, remaining samples will be stored for use in future Human Research Ethics Committee approved hepatitis C related research. Additional consent will not be sought for this storage and future use. It is not optional.

Participants not wishing to have their samples stored or used in future hepatitis C related research will not be eligible to participate in this study.

10.0 Statistics

10.1 Sample Size

The study is designed to enrol a total of 375 patients: 125 in the standard arm and 250 in the simplified arm. The primary efficacy endpoint of SVR12 will be assessed within each arm, and the primary comparison of SVR12 rates will be for non-inferiority of standard to simplified arms. With these patient numbers, the study has approximately 80% power to show non-inferiority to standard treatment monitoring with a lower confidence bound for the difference (standard – simplified) in SVR12 rates greater than –6% (assuming an SVR12 rate of 96% in both arms).

10.2 Assessments of efficacy

A final full statistical analysis plan will be written and signed off by the Protocol Steering Committee prior to final study data lock.

Primary endpoints:

1. SVR12 defined as the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment (week 20) based on ITT population.

Secondary endpoints:

2. SVR12 defined as the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment (week 20) based on mITT population.
3. Proportion adherent to treatment and study visits (on-treatment adherence and early treatment discontinuation);
4. Change in health-related quality of life during treatment (measured by EG-5D-3L);
5. Resistance associated substitutions (RAS): SVR12 in participants with and without baseline RAS, and RAS distribution in participants with virological failures;
6. Patient treatment satisfaction measured by a questionnaire applied to all participants;

Exploratory endpoint:

7. Provider acceptability of simplified monitoring strategy.

10.3 Efficacy analysis

The primary analysis will compare the randomised treatment arms on an ITT basis (see section 10.4). The primary efficacy endpoint is the proportion of patients with undetectable HCV RNA at 12 weeks post end of treatment. The treatment arms will be considered non-inferior if the lower limit 95% CI of the difference between the two arms does not exceed -6%. There will be no extrapolation of data for the primary endpoint. Patients with missing data will be analysed as missing equals failure. Secondary analyses will compare randomised treatment groups based on available data (mITT Population).

For all secondary endpoints simple pairwise comparisons of the randomised treatment arms will be undertaken for both the ITT and mITT populations.

10.4 Assessments of safety

Safety endpoint:

8. Proportion of patients with common adverse events (reported in greater than 5%).
9. Proportion of patients with at least one severe or potentially life threatening (grade 3 or 4) adverse event.
10. Proportion of patients with un-scheduled clinic visits.

Safety analyses will also be undertaken with the proportion of patients with Grade 3 or 4 adverse events, and grade adverse events will be summarised by randomised treatment group, by severity and relation to study drug. Serious adverse events will be summarised for all enrolled patients.

10.5 Definition of Intent-to-treat Population

Intent-to-treat (ITT) and modified intent-to-treat (mITT) populations will be used for efficacy analyses. All patients who receive at least one dose of study drug will be included in the ITT population (and safety population). The mITT population will exclude patients who have completed treatment (>95% adherence) (according to phone contact at week 8), but have not returned for their SVR12 assessment. The data from the ITT and mITT will be presented by the treatment arm assigned at the time of randomisation. For the primary analyses of non-inferiority tests, the percentage of patients achieving SVR12 in each arm will be calculated with confidence intervals (CI) using the normal approximation to the binomial distribution.

10.6 Definition and evaluation of HCV resistance

Regions encoding NS3 and NS5A will be sequenced from available baseline samples from all patients, and from the first available post-baseline sample with HCV RNA ≥1000 IU/mL from patients with virologic failure. Baseline polymorphisms relative to a subtype-specific reference sequence for all patients, and

treatment-emergent substitutions relative to the patient's baseline sequence for patients with virologic failure will be identified using the following set of amino acid positions: 36, 43, 54, 55, 56, 80, 155, 156, 166, 168 in NS3; 24, 28, 29, 30, 31, 32, 58, 92, 93 in NS5A. These are positions at which substitutions have been observed in vitro or clinically in NS3 or NS5A in any genotype with drugs for the respective inhibitor class.

11.0 Data Safety and Monitoring Board (DSMB)

A data safety and monitoring board (DSMB) will consist of at least 1 statistician and 2 practicing gastroenterologist/infectious diseases specialists. The meeting will include the interim safety and adherence analysis which will be performed when the first 75 participants have either completed SVR12 or dropped out of the study. Additional DSMB meetings will be scheduled at a frequency commensurate with the risk as determined by the DSMB.

12.0 Data collection, source documents and record retention

The Principal Investigator and the institution where the study will be conducted will permit study-related monitoring, audits, ethics committee review and regulatory inspection providing direct access to source documents.

Data will be collected on study specific electronic or paper copy case record forms. The Principal Investigator is responsible for ensuring the data collected are complete, accurate and recorded in a timely manner.

12.1 Submission of data

Electronic CRFs: following each participant visit the designated site staff will complete the visit specific eCRF. Once all required information is received the eCRF shall be considered complete. Project Team staff will then monitor the data for completeness and accuracy. Any eCRF discrepancies, either manual or automatic, will be addressed with the site staff for clarification.

The site Principal Investigator is responsible for ensuring the completion of accurate source documentation to support data collected on case report forms. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the trial. Source documents include, but are not limited to; participant medical records, laboratory reports, ECG tracings, X-rays, radiologist reports, participant diaries, biopsy reports, ultrasound images, participant progress notes, pharmacy records and any other reports or records of procedures performed in accordance with the protocol.

It is not acceptable for the CRF to be the only record of study participation and progress must also be recorded in the each person's medical record. This is to ensure that anyone accessing the medical record has adequate knowledge that the person is a clinical trial participant.

Any document that acts as a source document (the point of the initial recording of a piece of data) should be signed and dated by the person recording or reviewing the data for issues of medical significance (for example the review of laboratory reports). Persons signing the source documents must be listed as a site staff member.

The sponsor's monitor will visit sites to conduct source document verification. The number of visits will depend upon study complexity and recruitment rate; however, the monitor will conduct a minimum of three source data verification visits during the study. Ideally the first will occur shortly after randomisation of the first participant(s), the second during study conduct and the final following completion of all study visits. Additional monitoring visits may be scheduled if required.

The Principal Investigator is responsible for retaining all essential documents listed in ICH Good Clinical Practice guidelines. These must be organised in a comprehensive filing system that is accessible to study monitors and other relevant personnel.

12.2 Archiving

The Principal Investigator is responsible for ensuring all study documents are retained for a minimum of 15 years following completion and publication of the study or for the duration required by the local regulatory authority.

13.0 Ethics committee/regulatory approval and informed consent

The sponsor is responsible for ensuring regulatory approval for the study is obtained.

The site Principal Investigator is responsible for obtaining IRB/EC approval for the protocol and participant information and informed consent form in compliance with local regulatory requirements prior to entering any participant into the study. The approval letter/document must clearly identify the protocol and all documents approved by the IRB/EC including version number & date of the protocol and participant information and consent form. A copy of the approval document must be sent to the study sponsor.

The site Principal Investigator must also obtain approval for any amendments to the protocol or participant information and informed consent form. The Principal Investigator must comply with all IRB/EC reporting requirements for all adverse events, annual updates and end of study reports and must agree to abide by any IRB/EC conditions of approval.

The site Principal Investigator (or designee) is responsible for ensuring freely-given consent is obtained from each potential participant prior to the conduct of any protocol-specific procedures. The Principal Investigator may delegate the task of obtaining consent to appropriately qualified Sub-investigator(s). Consent must be documented by the participant's dated signature on the participant information and consent form together with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated participant information and consent form must be given to the person prior to study participation. The participant or their legally authorised representative must be informed in a timely manner of any new information that becomes available during the course of the study that may affect his/her willingness to continue study participation.

This study shall be conducted in accordance with the ethical principles laid out in the Declaration of Helsinki (most current issued version) and the National Statement on Ethical Conduct in Research Involving Humans (most current issued version).

14.0 Confidentiality of data

14.1 Confidentiality of participant records

By signing the Clinical Trial Agreement, the site Principal Investigator agrees that the sponsor, IRB/EC or regulatory authorities may consult and/or copy study documents to verify information in the case report form. By signing the consent form the participant agrees to these processes.

Participant confidentiality will be maintained at all times and no documents containing the participant's name or other identifying information will be collected by the sponsor. It may be necessary for the sponsor's representatives, the IRB/EC and regulatory authority representatives to have direct access to the participant's medical records. If study documents need to be photocopied during the process of verifying case report form data, the participant will be identified by a unique code only; full names and other identifying information will be masked.

14.2 Confidentiality of study data

By signing the Clinical Trial Agreement, the site Principal Investigator affirms to the sponsor that information provided to them by the sponsor will be maintained in confidence and divulged only as necessary to the ethics committee and institution employees directly involved in the study. Both ethics committee members and employees must also understand the confidentiality requirements for any information divulged to them. The data generated by this study will be considered confidential, except where it is included in a publication as agreed in the publication policy of this protocol.

At sites where regulations restrict the collection of full date of birth and/or initials, the following conventions will be used:

- Date of birth will be entered as 01/01/YYYY
- Initials will be entered as AA-AA, BB-BB, CC-CC etc.

15.0 Governance

This research protocol is sponsored by UNSW Sydney with funding and provision of study drug by AbbVie Pty LTD. The study is coordinated through the Kirby Institute for Infection and Immunity in Society, UNSW Australia. The Kirby Institute has established governance and implementation structures which use resources efficiently to deliver program objectives on schedule.

16.0 Quality Control (QC) and Quality Assurance (QA)

The sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice standards and all applicable local laws and regulations relating to the conduct of a clinical trial.

17.0 Publication Policy

The results of this study may be published and presented at scientific meetings. Publication of data derived from this protocol will be governed by the Protocol Steering Committee. All published data will be non-identifiable grouped data and will follow the guidelines set forth by the International Committee of Medical Journal Editors (ICMJE).

18.0 List of References

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4. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial.[comment]. *Lancet* 2001; **358**(9286): 958-65.

5. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *The New England journal of medicine* 2011; **364**(25): 2405-16.

6. Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *The New England journal of medicine* 2011; **364**(13): 1195-206.

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19.0 Abbreviations List

ACD	Acid Citrate Dextrose
AE	Adverse Event
ALT	Alanine Aminotransferase
APRI	AST to Platelet Ratio Index
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
CI	Confidence interval
DAA	Direct Acting Antiviral
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDTA	Ethylenediamine Tetraacetic Acid
EOT	End of Treatment
FBC	Full Blood Count
FPFV	First Patient First Visit
GGT	Gamma Glutamic Transpeptidase
HBC	Hepatitis B Virus
HCV	Hepatitis C Virus
Hgb	Haemoglobin
HIV	Human Immunodeficiency Virus
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LFTs	Liver Function Tests
LLN	Lower Limit of Normal
LLOQ	Lower Limit Of Quantification
LPLV	Last Patient Last Visit
mITT	Modified intent-to treat
PEG-IFN	Pegylated interferon alfa 2a/b
PBMC	Peripheral Blood Mononuclear Cell
RAS	Resistance Associated Substitutions
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR12	Sustained Virological Response (HCV RNA undetectable 12 weeks post-treatment)
UDS	Urinary Drug Screen
ULN	Upper Limit of Normal
UNSW	University of New South Wales
WCC	White Cell Count
WOCBP	Women of Childbearing Potential