A randomised study of interferon-free treatment for recently acquired hepatitis C in people who inject drugs and people with HIV coinfection (REACT)

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Protocol Synopsis

Title	A randomised study of interferon-free treatment for recently acquired hepatitis C in people who inject drugs and people with HIV coinfection (REACT)
Protocol registration number:	NCT 02625909
Background and rationale	Globally, 3-4 million new hepatitis C virus (HCV) infections are estimated to occur annually (1). People who inject drugs (PWID) represent one of the groups at highest risk of transmitting and acquiring infection with the majority of new (60%) and existing (80%) infections in developed countries occur in this population with HCV antibody prevalence estimated at 67% (60-80%) (2, 3). HIV-positive men-who-have-sex-with-men (MSM) are another high risk group for HCV acquisition. The advent of DAAs has changed the therapeutic landscape for individuals with chronic HCV infection with IFN-free therapy offering high efficacy and tolerability, even in "difficult-to-treat" populations (4-11). Multiple agents in different classes have been approved in Australia by the Therapeutic Goods Administration (TGA), the European Union by the European Medicines Agency (EMA), the US by the Food and Drug Administration (FDA), and in Canada by Health Canada Given the burden of HCV-related disease among PWID and HIV-positive MSM, strategies to enhance HCV assessment, treatment and prevention in these groups are urgently needed. Much of what is known about the timing of treatment initiation, regimen choice and duration of therapy in acute HCV infection comes from small observational studies and randomized controlled trials in selected populations with limited data on treatment in PWID and HIV co-infection. With recent rapid advances in HCV therapeutics, management strategies for acute HCV will evolve rapidly over the next few years. The REACT study will compare the efficacy and safety of sofosbuvir/velpatasvir administered for 6 or 12 weeks in individuals with recent HCV infection. The role and activity of potent DAA regimens in acute HCV infection requires evaluation, with the potential to be given as highly efficacious, short course IFN-sparing regimens, maximising acceptability to patients, encouraging uptake of treatment, limiting further transmission and preventing progression to chronic liver disease.

	Refer to Section 1.0 for complete background and rationale.
Study objectives	**Hypothesis** Six weeks treatment with sofosbuvir/velpatasvir is non-inferior to twelve weeks treatment with sofosbuvir/velpastavir as assessed by sustained virological response at 12 weeks post treatment in the intention-to-treat population (SVR12). **Primary objective** The primary objective is to evaluate the proportion of patients with HCV RNA below the level of quantitation (target not detected [TND] or target detected, not quantifiable [TDnq]) at 12 weeks post end of treatment (SVR12) following sofosbuvir/velpatasvir therapy for 6 weeks (short treatment duration) as compared with 12 weeks (standard treatment duration) in people with recent HCV infection (duration of infection ≤12 months). **Secondary objectives** 1 To evaluate the proportion of participants with HCV RNA below the level of quantitation (TND or TDnq) at the end of treatment (ETR), 4 weeks after treatment completion (SVR4) and 24 weeks after treatment completion (SVR24); 2 To evaluate the proportion of participants with undetectable HCV RNA through 2 years post treatment; 3 To evaluate the levels of adherence, factors associated with suboptimal adherence including HIV status, and the impact of suboptimal adherence on therapeutic response; 4 To evaluate the impact of treatment on illicit drug use, injecting behaviour and sexual risk taking behaviour (behavioural survey) during treatment; 5 To evaluate safety and tolerability 6 To evaluate the change in HIV RNA and CD4 (on-treatment and end of treatment); 7 To evaluate the rate and risk factors for reinfection during and up to 2 years following treatment; 8 To evaluate the immunological factors associated with treatment induced clearance and reinfection 9 To evaluate patient interest and attitudes towards long acting parenteral hepatitis C therapy (Long-Acting Hepatitis C Therapy Questionnaire)

Participant population	A total of 250 participants with recent HCV infection will be enrolled from drug and alcohol clinics, tertiary liver and infectious diseases clinics and community health centres across Australia, Canada, Germany, New Zealand, Switzerland, The Netherlands, the United Kingdom and the United States. The Kirby Institute may close or suspend screening prior to reaching 250 participants in order to manage the total study enrolment numbers. The number of participants with HCV/HIV coinfection enrolled to the study will be capped at 70% (or less than 175 participants) of the total study population. In addition, the number of participants with HCV reinfection enrolled to the study will be capped at 20% (or less than 50 participants) of the total study population. **Inclusion Criteria** Subjects must meet all of the following inclusion criteria to be eligible to participate in this study. 1 Participants have voluntarily signed the informed consent form. 2 18 years of age or older. 3 Detectable HCV RNA at screening (>10,000 IU/ml), and in the opinion of the investigator is unlikely to demonstrate spontaneous viral clearance 4 HCV genotypes 1-6. 5 HBsAg negative 6 Negative pregnancy test at screening and baseline (females of childbearing potential only). 7 Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception 8 Medically stable on the basis of physical examination, medical history and vital signs 9 Adequate literacy to provide reliable responses to the study questionnaires 10 All fertile males and females must be using effective contraception during treatment and during the 30 days after treatment end. 11 Recently acquired HCV infection (estimated duration of infection ≤12 months)*

	Recently acquired HCV infection as defined by: A) i) First anti-HCV Ab or HCV RNA positive within the previous 6 months and ii) Documented anti-HCV Ab negative within the 12 months prior to anti-HCV antibody positive result OR B) i) First anti-HCV Ab or HCV RNA positive within the previous 6 months and ii) Acute clinical hepatitis (jaundice or ALT> 10 X ULN) within the previous 6months prior to first positive HCV antibody or HCV RNA, with no other cause of acute hepatitis identifiable OR C) For cases of recent HCV reinfection the following criteria are required: i) Documented prior HCV antibody positive with HCV RNA negative on at least 2 occasions 6 months apart **and** ii) new HCV RNA positive within the previous 6 months *Estimated duration of infection based on midpoint between last antibody negative or HCV RNA and first antibody positive or HCV RNA in the case of seroconversion and 6 weeks prior to date of maximum ALT in the case of acute hepatitis. See Section 3.4 for 'Definitions used to calculate Estimated Date of Infection'. If co-infection with HIV is documented, the subject must meet the following criteria: 1 Antiretroviral (ARV) untreated for >8 weeks preceding screening visit with CD4 T cell count >500 cells/mm^3 OR

	2 On a stable ARV regimen for >8 weeks prior to screening visit, with CD4 T cell count >200 cells/mm^3 and an undetectable plasma HIV RNA level. • Suitable ARV include: o Nucleos(t)ide reverse transcriptase inhibitors: Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), emtricitabine (FTC)Non-nucleoside reverse transcriptase inhibitors: Rilpivirine o Protease inhibitors: Atazanavir, darunavir, lopinavir, ritonavir o Integrase inhibitors: Dolutegravir, raltegravir, elvitegravir/cobicistat • Contraindicated ARV include: o Efavirenz ▪ 50% reduction in velpatasvir (GS-5816) exposure o Didanosine o Zidovudine o Tipranavir Other ARV agents may be permissible at the time of study commencement pending further drug-drug interaction studies; please discuss with the Medical Monitor. **Exclusion criteria** Subjects 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. History of chronic pulmonary disease associated with functional limitation, severe cardiac disease, major organ transplantation or other evidence of severe illness, malignancy, or any other conditions which would make the patient, in the opinion of the investigator, unsuitable for the study c. Solid organ transplant d. Malignancy within 5 years prior to screening, with exception of specific cancers that may have been cured by surgical resection (basal cell skin cancer, etc.). Subjects under evaluation for possible malignancy are also excluded. e. Significant drug allergy (such as anaphylaxis or hepatotoxicity). 2 Subject has a known or documented prior history of cirrhosis

	3 Subject shows evidence of significant liver disease in addition to hepatitis C, which may include but is not limited to drug- or alcohol-related cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson's disease, non-alcoholic steatohepatitis (NASH), or primary biliary cirrhosis 4 Any of the following lab parameters at screening: a. Direct bilirubin > 1.5 x ULN b. Platelets < 50,000/µL c. Creatinine clearance (CL_{cr}) < 50 mL/min d. Haemoglobin < 10 g/dL e. Albumin < 30g/L f. International Normalised Ratio (INR) >1.5 (unless subject is on a stable anticoagulant regimen or has known coagulopathy) 5 Pregnant or nursing female. 6 Use of prohibited concomitant medications as described in section 5.2 7 Chronic use of systemically administered immunosuppressive agents (e.g. prednisone equivalent > 10 mg/day) 8 Known hypersensitivity to velpatasvir, sofosbuvir or formulation excipients. 9 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. 10 Any investigational drug ≤6 weeks prior to the first dose of study drug. 11 Previous failure of therapy with sofosbuvir or an NS5A inhibitor prior to the first dose of study drug. 12 Ongoing severe psychiatric disease as judged by the treating physician. 13 Frequent injecting drug use that is judged by the treating physician to compromise treatment safety. 14 Inability or unwillingness to provide informed consent or abide by the requirements of the study. 15 Prior enrolment within this study.
Study design	This study will be conducted as a phase III randomised, open-label, non-inferiority multicentre international trial. A total of 250 people with recently acquired hepatitis C will be enrolled and randomised. The study consists of a screening phase (-12 to -4 weeks), treatment commencement from baseline, randomisation between week 5 and 6, treatment for another 6 weeks for those randomised to standard therapy (12 weeks of treatment) or end of treatment for those randomised to shortened treatment (6 weeks of treatment). Randomisation will be using blocks and will be stratified by study site and HIV status.

	All participants will then enter the follow-up phase (96 weeks) to evaluate treatment response and reinfection. Participants who become re-viraemic following an end of treatment response will be followed monthly for six months. After completing the monthly follow-up visits, participants will continue to attend three monthly follow-up visits up to two years. Please see section 7 'Reinfection follow-up' for more details.
Treatment of participants	Participants will receive six or twelve 12 weeks of open-label sofosbuvir/velpatasvir (400mg/100mg daily) in an oral once-daily fixed dose combination. Dose modifications are prohibited.
Study procedures	All participants will complete screening, on-treatment and post-treatment assessments as outlined in the Schedule of Assessments in Section 6.0. Screening assessments must be completed within 12 weeks prior to baseline. There must be a minimum of 4 weeks between screening and baseline. Following screening, eligible participants will commence treatment at baseline. Between week 5 and week 6, participants will be randomised to the shortened or standard treatment duration. On-treatment visits will be conducted at weeks 1, 2, 4 and 6 (end of treatment for participants on shortened treatment duration), weeks 8 and 10 (for participants on standard treatment duration only). Participants on standard treatment duration will attend end of treatment at week 12. For participants randomised to shortened treatment, follow-up visits will be conducted at week 10 (SVR4), week 18 (SVR12), week 30 (SVR24), week 42 (FU1), week 54 (FU2), week 66 (FU3), week 78 (FU4), week 90 (FU5) and week 102 (Termination). For participants randomised to standard treatment, follow-up visits will be conducted at week 16 (SVR4), week 24 (SVR12), week 36 (SVR24), week 48 (FU1), week 60 (FU2), week 72 (FU3), week 84 (FU4), week 96 (FU5) and week 108 (Termination).

Statistics	The primary objective of this trial is to establish the non-inferiority of short duration treatment (6 weeks) to the standard duration treatment (12 weeks). Assuming an expected SVR of 90% in the control arm, 113 participants per arm will be required to give 80% chance that the two sided confidence interval of the difference between regimens has a lower limit greater than -12**%.** A total of 250 subjects enrolled and randomised will comprise the intention-to-treat (ITT) population and will form the study population for evaluation of the primary and secondary endpoints. **Primary endpoint:** The primary endpoint is the proportion of participants with HCV RNA below the level of quantitation (target not detected [TND] or target detected, not quantifiable [TDnq]) at 12 weeks post end of treatment (SVR12) **Secondary endpoints:** • Secondary virological endpoints ○ The proportion of participants with: • ETR defined as HCV RNA below the level of quantitation at end of therapy • SVR 4 defined as HCV RNA below the level of quantitation 4 weeks post therapy • SVR 24 defined as HCV RNA below the level of quantitation 24 weeks post therapy • HCV RNA below the level of quantitation through 2 years post treatment Results will be stratified by HCV genotype and HIV-coinfection. • 80/80 adherence: Defined as the receipt of >80% of scheduled doses for >80% of the scheduled treatment period. • 90/90 adherence: Defined as the receipt of >90% of scheduled doses for >90% of the scheduled treatment period. • 100/100 adherence: Defined as the receipt of 100% of scheduled doses for 100% of the scheduled treatment period. • On-treatment adherence: Calculated by subtracting the number of missed doses from the total number of doses of scheduled treatment and dividing by the total intended therapy duration. This measures the proportion of doses received from the time that treatment was initiated until treatment was discontinued or completed. • Toxicity: Proportion of participants with at least one severe or potentially life threatening (grade 3 or 4) adverse event.

	• Early treatment discontinuation: Discontinuation of therapy prior to the per-protocol planned end of treatment (6 or 12 weeks depending on study arm). • Resistance associated variants (RAVs): The proportion of treated subjects with development of RAVs following virological relapse or breakthrough. • Reinfection rate: Rates of HCV reinfection will be calculated using person-time of observation during and up to 48 months following end of treatment. • Baseline characteristics, on-treatment adherence, risk behaviours and toxicity will be evaluated among subjects withdrawing prior to randomisation.

Schedule of Assessments

Arm A: Short – 6 weeks

Assessment/Procedure	Screening#	Baseline	Study Treatment (weeks)				Follow-up (weeks)								
Study week	**-12 to -4**	**0**	**1**	**2**	**4**	**6 (ETR)**	**10 (SVR4)**	**18 (SVR12)**	**30 (SVR24)**	**42 (FU1)**	**54 (FU2)**	**66 (FU3)**	**78 (FU4)**	**90 (FU5)**	**102 (Termination)**
Visit Window (Days)			**+/- 3**	**+/- 3**	**+/- 3**	**+/- 3**	**+/- 3**	**+/- 14**	**+/- 14**	**+/- 28**	**+/- 28**	**+/- 28**	**+/- 28**	**+/- 28**	**+/- 28**
Informed consent, medical history, physical examination	x														
Patient demographics	x														
Vital signs & physical measurements	x	x													
Randomisation[g]						x									
FibroScan®	x							x	x	x	x	x	x	x	x
Anti-HCV antibody	x														
HCV-RNA testing (local lab.)	x	x				x		x	x	x	x	x	x	x	x
HCV Genotype	x														
Liver function tests/Full blood count/Biochemistry	x	x	x	x	x	x	x	x	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]
Clotting (INR)	x														
HIV[a], HBV & HAV serology	x														
CD4/CD8 & HIV viral load[b]	x							x	x	x	x	x	x	x	x
Pregnancy test (serum or urine)[c]	x	x			x		x								
Behavioural questionnaire	x	x				x		x	x	x	x	x	x	x	x
Adherence questionnaire				x	x	x									
Pill count				x	x	x									
Health outcomes survey (EQ-5D)	x							x							
Concomitant medications	x	x	x	x	x	x									
Adverse events		x	x	x	x	x	x								
Long-Acting Hepatitis C Therapy Questionnaire		x[h]													
Research Specimen Collection															
EDTA plasma (10ml)	x[d]	x[d]	x	x	x	x	x	x	x	x	x	x	x	x	x
Whole blood (4ml)	x	x													
ACD Plasma / PBMCs (60ml)	x	x	x	x	x	x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]

[#] Minimum wait period between screening and baseline visit is 4 weeks, [a] HIV negative individuals only, [b] HIV positive individuals only, [c] Females of child bearing potential only, [d] 20ml collected at screening and baseline, [e] To be collected in patients with suspected relapse/reinfection, [f] Liver function tests only, [g] randomisation will occur between week 5 and 6, [h] Currently enrolled participants will complete questionnaire at their next scheduled visit

Arm B: Standard – 12 weeks

Assessment/Procedure	Screening#	Baseline	Study Treatment (weeks)							Follow-up (weeks)								
Study week	**-12 to -4**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12 (ETR)**	**16 (SVR4)**	**24 (SVR12)**	**36 (SVR24)**	**48 (FU1)**	**60 (FU2)**	**72 (FU3)**	**84 (FU4)**	**96 (FU5)**	**108 (Termination)**
Visit Window (Days)			**+/- 3**	**+/- 3**	**+/- 3**	**+/- 3**	**+/- 3**	**+/- 3**	**+/- 3**	**+/- 3**	**+/- 14**	**+/- 14**	**+/- 28**	**+/- 28**	**+/- 28**	**+/- 28**	**+/- 28**	**+/- 28**
Informed consent, medical history, physical examination	x																	
Patient demographics	x																	
Vital signs & physical measurements	x	x																
Randomisation						x												
FibroScan®	x										x	x	x	x	x	x	x	x
Anti-HCV antibody	x																	
HCV-RNA testing (local lab.)	x	x							x		x	x	x	x	x	x	x	x
HCV Genotype	x																	
Liver function tests/Full blood count/Biochemistry	x	x	x	x	x	x	x	x	x	x	x	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]	x[f]
Clotting (INR)	x																	
HIV[a], HBV & HAV serology	x																	
CD4/CD8 & HIV viral load[b]	x								x		x	x	x	x	x	x	x	x
Pregnancy test (serum or urine)[c]	x	x			x		x		x	x								
Behavioural questionnaire	x	x				x			x		x	x	x	x	x	x	x	x
Adherence questionnaire				x	x	x	x	x	x									
Pill count				x	x	x	x	x	x									
Health outcomes survey (EQ-5D)	x										x							
Concomitant medications	x	x	x	x	x	x	x	x	x									
Adverse events		x	x	x	x	x	x	x	x	x								
Long-Acting Hepatitis C Therapy Questionnaire		x[h]																
Research Specimen Collection																		
EDTA plasma (10ml)	x[d]	x[d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Whole blood (4ml)	x	x																
ACD Plasma / PBMCs (60ml)	x	x	x	x	x	x			x	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]	x[e]

[#] Minimum wait period between screening and baseline visit is 4 weeks, [a] HIV negative individuals only, [b] HIV positive individuals only, [c] Females of child bearing potential only, [d]20ml collected at screening and baseline, [e] To be collected in patients with suspected relapse/reinfection, [f] Liver function tests only, [g] randomisation will occur between week 5 and 6, [h] Currently enrolled participants will complete questionnaire at their next scheduled visit

1 Background and rationale

1.1 Incidence and risk factors for HCV acquisition

Globally, 3-4 million new hepatitis C virus (HCV) infections are estimated to occur annually (1). People who inject drugs (PWID) represent one of the groups at highest risk of transmitting and acquiring infection with the majority of new (60%) and existing (80%) infections in developed countries occur in this population with HCV antibody prevalence estimated at 67% (60-80%) (2, 3). HIV-positive men-who-have-sex-with-men (MSM) are another high risk group for HCV acquisition.

In the United States, HCV incidence fell between 2006 and 2010, although subsequently rose to 0.6 per 100,000 in 2012 (12, 13). However, US surveillance relies upon passive reporting (with the exception of 6 US jurisdictions funded for enhanced surveillance between 2006–2011) (13) thus leading to a marked underestimate of the true incidence. Mathematical modelling suggests that the incidence of new HCV infections is in the region of 5-10 times greater than reported. Recent estimates following enhanced surveillance suggest that 17,100-21,870 new infections occur annually in the US (approximately 12.3 infections per reported case) (13, 14).

In Europe, 7.3–8.8 million people (1.1–1.3%) were estimated to be living with chronic HCV infection (15), with injecting drug use (IDU) accounting for the majority (60–90%) of prevalent cases (16). Incident cases were estimated at 6.2 per 100,000 people in 2005 (15), though significant regional variation existed with many countries in Eastern Europe documenting a recent increase in IDU with an associated rise in HCV incidence and prevalence (17).

In Australia, approximately 5000 newly acquired cases are notified each year through national surveillance systems (18), with 90% of these cases occurring as a result of unsafe injecting practices (18, 19). Mathematical models estimate that the true number of new HCV infections peaked at 14,000 cases per annum in 1999 (20) before falling to 5,400-8,790 cases in 2013 for an incidence of 0.04 per 100,000 (18, 21). The decline in incidence was largely attributed to a reduction in IDU.

Although overall HCV incidence is falling in many countries, high incidence persists in specific populations, including young adult PWID (12, 13, 18, 22-24), incarcerated PWID (25) and HIV-positive MSM. Over the last decade, an international epidemic of acute HCV infection has been observed in HIV-positive men-who-have-sex-with-men (MSM), largely associated with sexual and non-IDU behaviour (26-33). In the Swiss Cohort Study, HCV incidence increased 18-fold in MSM between 1998-2011, while it declined in PWID and remained <1 per 100 py in heterosexuals (27). As compared with PWID, risk factors for HCV acquisition in MSM include unprotected anal intercourse, higher number of sexual partners, group sex, ulcerogenital sexually transmitted diseases (notably syphilis and lymphogranuloma venereum) and sexual acts that involve trauma and bleeding (27, 32, 33). However, while non-IDU is associated with this epidemic, concurrent IDU remains an important mode of HCV acquisition (26) and places this population at greater risk. In a cohort study of HIV-infected MSM, significantly higher incidence was documented among PWID as compared with non-PWID (4.7 per 100 py [95% CI: 2.7, 7.5] vs 0.6 per 100 py [95% CI: 0.4, 0.8]; HR 8.7 [95% CI: 4.6, 16.6]; p <0.001) (31).

1.2 Management of chronic HCV infection - directly acting antiviral therapy

The advent of DAAs has changed the therapeutic landscape for individuals with chronic HCV infection with IFN-free therapy offering high efficacy and tolerability, even in "difficult-to-treat" populations (4-11). Multiple agents in different classes have been approved in Australia by the Therapeutic Goods Administration (TGA), the European Union by the European Medicines Agency (EMA), the US by the Food and Drug Administration (FDA), and in Canada by Health Canada.

One such agent is the NS5B polymerase inhibitor, sofosbuvir (SOF). This drug belongs to the nucleotide analogue class of polymerase inhibitors, which mimics and competes with the natural nucleotides resulting in chain termination and prevention of viral replication. SOF targets the highly conserved active site of the HCV-specific NS5B polymerase, an effect that is independent of the viral genotype. As such, it is highly potent, has pan-genotypic activity and a high barrier to resistance. Its activity has been assessed in a number of Phase II and III trials in combination with PEG-IFN, RBV and/or an NS5A inhibitor, including those with HIV co-infection (6, 7, 34-39).

SOF in combination with velpatasvir (GS-5816), a 2nd generation NS5A inhibitor, is currently completing Phase III evaluation in the ASTRAL program. As individual agents, SOF and velpatasvir exhibited potent pan-genotypic (GT 1a, 1b, 2a, 2b, 3a, 4a, 5a, 6a) anti-HCV activity with additive antiviral interaction when co-adminstered. The regimen has been well tolerated and is effective. In an ongoing Phase 2 trial, treatment-naïve, non-cirrhotic individuals with genotypes 1-6 HCV infection received 12 weeks of SOF plus GS-5816, dosed at either 25 mg or 100 mg daily. SVR12 was 95% (73/77) in those receiving the 25 mg dose and 96% (74/77) in those receiving the 100 mg dose (40). Shorter treatment durations have been studied. Treatment-naïve, non-cirrhotic individuals with HCV GT 1 and 2 were randomised to SOF+GS-5816 (25mg or 100mg) with or without RBV for 8 or 12 weeks (41). In those receiving 12 weeks without RBV, SVR12 was 96-100% in those with GT 1 (GS-5816 25mg: 26/27; GS-5816 100mg: 28/28) and 91-100% in those with GT 2 (GS-5816 25mg: 10/11; GS-5816 100mg: 10/10) (41). In ELECTRON2, 104 treatment-naïve, non-cirrhotic individuals with GT 3 HCV infection were randomised to SOF+GS-5816 25 mg, SOF+GS-5816 25 mg+RBV, SOF+GS-5816 100 mg, or SOF+GS-5816 100 mg+RBV for 8 weeks with SVR 12 100% (27/27), 88% (21/24), 96% (26/27) and 100% (26/26), respectively (42).

Reduced susceptibility to SOF is associated with the NS5B substitution S282T. However, the clinical significance of the mutation is limited as the presence of S282T reduces viral replication capacity by 89-99% as compared with wild type virus. In a pooled analysis of subjects who received sofosbuvir in 4 phase III clinical trials (SOF + RBV +/- PEG), no resistance was detected by deep sequencing in any individual with virologic failure(43). One patient who relapsed at week 4 post-treatment following 12 weeks of SOF monotherapy in the phase II ELECTRON trial demonstrated the S282T mutation. However, by week 12 post-treatment, the mutation was no longer detectable by next generation sequencing, consistent with the impaired replicative capacity of the mutant strain(44). Moreover, retreatment with SOF-containing regimens is successful in SOF-experienced patients (45, 46). No on-treatment resistance associated viral breakthrough has been observed and virtually all patients who have received SOF to date showed a robust and rapid response with suppression of HCV viraemia to undetectable levels within 2-4 weeks.

1.3 Management of recent HCV infection

1.3.1 Treatment of acute HCV mono-infection

Global clinical practice of acute HCV monoinfection is not standardised with significant uncertainty regarding the optimal regimen and treatment duration, particularly as the therapeutic landscape changes with the advent of directly-acting antiviral (DAA) therapy for chronic HCV. Previous international guidelines had been in agreement regarding administration of 16-24 weeks of PEG-IFN monotherapy (47) (48). However, despite the lack of direct evidence, recent amendments to the US guidelines support "the same regimens recommended for chronic HCV infection … owing to high efficacy and safety" (class IIa, level C) with PEG-IFN with or without RBV for 16-24 weeks listed as an alternative regimen (class II, level A) (48).

Early clinical trials evaluating standard or PEG-IFN monotherapy for acute HCV mono-infection demonstrated promising results (largely in symptomatic patients) with SVR 24 rates ranging from 75-98% (49-52). The first large prospective study evaluated 44 patients (mean duration of infection before treatment initiation: 89 days; GT 1, 61%) who received daily standard IFN alfa-2b for 4 weeks, followed by thrice weekly IFN for a further 20 weeks with a resultant SVR 24 of 98% (49). Santantonio et al administered 24 weeks of PEG-IFN alfa-2b to 16 patients with detectable HCV RNA 12 weeks following the onset of acute HCV infection with a resultant SVR 24 of 94% (51). In a larger German prospective trial, 89 patients (median duration of infection: 76 days) received PEG-IFN alfa-2b for 24 weeks with an SVR 24 of 71% in the ITT population (per-protocol SVR 24 89%) (53). A meta-analysis by Corey et al of 22 studies (including 1075 patients) revealed an overall SVR of 78% for acute HCV treated with standard or PEG-IFN monotherapy for a mean treatment duration of 19.7 weeks (standard deviation, 12.5 weeks) (54).

More recently, Santantonio et al evaluated the efficacy and safety of a 24 week course of PEG-IFN alfa-2b (group A) versus a 12-week course of PEG-IFN alfa-2b alone (group B) or with RBV (group C) in an open randomized multicentre trial involving 130 patients with acute HCV monoinfection who did not demonstrate spontaneous clearance after 12 weeks of observation (55). The study protocol excluded PWID. By ITT, the overall SVR 24 was 71.5%; the SVR 24 was 70.5% (31/44), 72.1% (31/43) and 72.1% (31/43) in groups A, B and C, respectively ($p = 0.898$). By per-protocol analysis, SVR 24 rose to 81.6% in each group. On multivariate analysis, a rapid virological response (RVR, undetectable HCV RNA at week 4 of treatment) was associated with SVR, consistent with the evidence available in chronic HCV infection. No other assessed baseline factor (age, gender, HCV genotype, treatment arm) predicted SVR.

The addition of RBV to PEG-IFN is of uncertain benefit in acute HCV mono-infection. The recent study by Santantonio et al (55) and others (56) demonstrate no additional advantage. In the Australian Trial in Acute Hepatitis C (ATAHC) trial, the addition of RBV in the HIV co-infected population improved viral kinetics as compared with PEG-IFN monotherapy in the HCV mono-infected population (57). Given the efficacy of RBV in chronic HCV infection, the treating clinician may consider adding RBV in an attempt to maximize SVR, in the absence of evidence.

1.3.2 Treatment of recent HCV infection in PWID

While the majority of HCV transmission in the developed world occurs in the setting of IDU, there are limited data on treatment of acute HCV infection in PWID. In a small Swiss study, 22 patients with acute HCV were assessed for treatment and 14 commenced PEG-IFN alfa-2b for 24 weeks (58). By ITT, the SVR 24 was 57%. However, adherence was poor with only 8 patients completing more than 80% of the scheduled treatment

course (SVR by per-protocol analysis, 88% [7/8]). De Rosa et al offered 12 weeks of directly observed therapy with PEG-IFN alfa-2b with a much improved SVR 24 of 74% (17/23) (59). Adherence was excellent with 96% (22/23) completing more than 80% of the scheduled treatment course.

The largest trial to date examining treatment of acute and early chronic HCV infection involving PWID was ATAHC, a multicentre prospective cohort study of the natural history and outcomes following treatment with PEG-IFN alfa-2a with or without RBV (60). Between 2004 and 2008, 167 subjects were enrolled, of whom 111 (76%) with detectable HCV RNA at screening elected to commence treatment. 57% of the treated population were GT 1, 85% had acquired HCV via IDU and the median estimated duration of infection was 25 weeks. 33% of subjects were HIV co-infected (predominantly sexual [permucosal] transmission). In the cohort of 74 HCV mono-infected individuals who commenced PEG-IFN monotherapy, the SVR 24 by ITT and per protocol analyses were 55% and 72%, respectively, with 77% (57/74) receiving at least 80% of the scheduled treatment course. While the SVR rate was lower in those who had a history of IDU (history of IDU, SVR 24 48% vs no IDU, SVR 24 91%, p = 0.03), after adjusted analysis, the only pre-treatment factors associated with treatment failure were poor social functioning and a history of drug dependency treatment.

Collectively, these data demonstrate that PWID with recent HCV infection can be treated successfully, but that strategies to optimize adherence in socially marginalized populations are required to improve outcomes.

While HCV treatment in PWID is feasible and successful across a broad range of multidisciplinary healthcare settings (58-61), treatment uptake remains low with multiple barriers to care at an individual and systems level, driven in part by concerns of adherence, social instability, treatment-related adverse effects, psychiatric comorbidity and the perceived risk of HCV reinfection (62). The availability of IFN-free, DAA therapy will address some of these concerns and may facilitate treatment uptake.

1.3.3 Treatment of recent HCV infection in HIV co-infection

While SVR rates with IFN-based therapy for chronic HCV in HIV co-infection have been consistently lower than those of HCV monoinfection, treatment efficacy is improved in acute HCV infection. In the ATAHC trial, 35 patients co-infected with HIV and HCV commenced 24 weeks of PEG-IFN and RBV with SVR 24 by ITT and per protocol analyses of 74% and 75%, respectively, higher than the HCV mono-infected population (60). The higher SVR among HIV-positive compared with HIV-negative individuals may relate to socio-demographic differences between these groups with the majority of HIV-positive individuals reporting higher levels of education and employment, more stable housing and greater social support than the HIV-negative patients, facilitating better adherence. Acknowledging the predominance of sexual (permucosal) transmission (60%), IDU remained an important mode of acquisition in the co-infected cohort (37%), with 54% reporting prior or current IDU (60).

Boescke et el demonstrated similar results with administration of either PEG-IFN alfa-2a monotherapy or PEG-IFN and RBV for 24-48 weeks at the investigators discretion (treatment duration 24 weeks: PEG-IFN 83%, PEG-IFN/RBV 70%) (63). The overall SVR was 64.8%, with no apparent additional benefit of RBV (PEG-IFN SVR 69%, PEG-IFN/RBV SVR 63%). The European AIDS Treatment Network (NEAT) reviewed nine co-infected cohorts, including 170 HIV-positive individuals who received IFN-based treatment for acute HCV infection (predominantly GT 1) and demonstrated a combined SVR 24 of 60-80% (64). Their subsequent

recommendations involve administration of 24-48 weeks of PEG-IFN and RBV, with treatment duration based on presence or absence of RVR.

1.3.4 Duration of treatment

The enhanced outcomes in early infection mean that IFN-based therapy at this time can often be simplified, and specifically be administered for a shorter duration. Previous studies have demonstrated the efficacy of short course treatment for 4 (SVR 24 87%) (50) and 12 weeks (SVR 24 72–74%) (50, 55, 61, 65, 66). Short duration response guided therapy may be appropriate for many individuals with recent HCV infection (67). Shorter treatment durations result in fewer adverse events, better quality of life, less frequent dose reductions and increased likelihood of optimal adherence (61, 65).

Shortening the duration of therapy with interferon-free DAA regimens in CHC is supported by recent phase II data. In LONESTAR, excellent results (SVR 12 95 – 100%) were obtained in GT 1 infection with 8 – 12 weeks of SOF and ledipasvir with or without RBV (4). SYNERGY proved that 6 weeks of triple combination DAA therapy is effective, with SVR 12 95% in arm B (SOF/ledipasvir plus GS-9669, a once-daily non-nucleoside NS5B inhibitor) and SVR 12 100% in arm C (SOF/ledipasvir plus GS-9451, a once-daily HCV NS3/4 protease inhibitor)(68). As double or triple DAA-combination regimens have markedly reduced treatment duration in GT 1 CHC as compared with standard of care (48 weeks PEG/RBV), it is postulated that similarly marked reductions in duration should be feasible in recently acquired HCV infection.

1.3.5 Directly-acting antiviral therapy for acute HCV infection

Very limited evidence exists for the use of DAA therapy in the setting of acute HCV infection. Fierer et al recently published the results of a pilot study involving administration of PEG-IFN, RBV and telaprevir in HIV-positive MSM with recent GT 1 HCV infection (69). Risk factors for acquisition were not reported. By ITT, SVR 12 was 84% (16/19). Treatment duration was response-guided; of those who achieved SVR 12, most (13/16; 81%) received ≤12 weeks of therapy. While these results are encouraging, the side-effect profile (70, 71), drug-drug interactions and treatment complexity seen with triple therapy regimens will likely prevent routine use of this strategy.

1.3.6 Reinfection following acute HCV infection

The risk of reinfection is often cited as a reason for not offering treatment to current and former PWID, but few studies have evaluated the incidence of HCV reinfection following successful treatment in this context. The limited evidence would suggest that the reinfection rate is low. Of 111 subjects treated in the ATAHC study, viral recurrence after treatment-induced suppression was observed in 19% (17/88) with 5 cases of reinfection (4.7 cases per 100 py; 95% CI 1.9, 11.2) (72). Ongoing IDU during follow up was reported by 38% of participants with treatment-induced virological suppression, with a higher reinfection rate in this subgroup (7.3 per 100 py [95% CI: 2.3, 22.6]). In the ATAHC Recall study, 50 individuals from the original ATAHC cohort were reassessed at a median duration of 7.2 years following primary infection with 37 (74%) having received treatment (SVR 24 70%) and 10 (20%) having demonstrated spontaneous clearance (73). Only 4 reinfections were identified (with 3 related to ongoing IDU) for an incidence rate of 1.8 per 100 py (95% CI: 0.7, 4.8). Importantly, significant changes were noted in injecting behaviour; 66% (33/50) had acquired HCV via IDU, but only 30% (15/50) reported ongoing use.

Two systematic reviews have examined the risk of reinfection in PWID after treatment-induced SVR, combining studies of acute and chronic HCV infection. In the first, the pooled estimate of reinfection from 5 prospective studies was 2.4 per 100 py (95% CI: 0.9, 6.1), rising to 6.4 per 100 py (95% CI: 2.5, 16.7) in those reporting ongoing IDU post SVR (74). The second systematic review and meta-analysis revealed similar findings with viral recurrence (late relapse or reinfection) in the "high risk" group (PWID, prisoners) estimated at 2.8 per 100 py (95% CI 2.06, 3.71) (75). Contrary to this, reinfection rates in predominantly young adult PWID who exhibited spontaneous clearance are higher, suggesting that this cohort may be at especial risk, though the number of subjects available for assessment was small (76-79).

Reinfection rates in HIV-positive MSM following primary HCV infection are varied, with very high incidence reported in some studies (80). In the aforementioned meta-analysis, viral recurrence (late relapse or reinfection) following SVR in those with HIV co-infection was 4.78 per 100 py (95% CI 3.97, 5.71) (75) . Multiple reinfections in individuals with ongoing high risk behaviour emphasise the need for continuing surveillance, education and prevention strategies (81, 82). In a retrospective analysis of 48 HIV-positive MSM with more than one sexually acquired HCV infection, 11 patients presented with 3 episodes and 1 patient with four episodes (81). In another cohort of HIV-positive MSM, the overall reinfection rate was 7.8 per 100 py (95% CI: 5.8, 10.5) with 8 individuals reinfected a second time for a secondary reinfection rate of 15.5 per 100 py (95% CI: 7.7, 31.0) (82).

1.4 ATAHC I, ATAHC II, DARE-C I and DARE-C II studies

The Australian Trial in Acute Hepatitis C (ATAHC) was an NIH funded multicentre prospective cohort study of the natural history, and outcomes following treatment with PEG (with or without RBV) in individuals with acute and early chronic HCV infection, with the final results published in Gastroenterology (60). Between 2004 and 2008, 167 subjects with acute and early chronic HCV infection were enrolled throughout Australia, of whom 111 (76%) subjects with detectable HCV RNA at screening elected to undertake treatment. 57% of the treated population were GT 1 and the median estimated duration of infection was 25 weeks, meaning that around half the patients had early chronic HCV infection. 33% of subjects were HIV co-infected. Final analysis of treatment outcomes in the 74 HCV mono-infected subjects who commenced treatment with PEG monotherapy demonstrated SVR rates of 55% and 72% by intention-to-treat and per-protocol analysis, respectively.

A second study (ATAHC II) was funded by the NIH for 5 years in 2010. One of the primary aims of this subsequent study is to explore potential therapeutic strategies aiming to enhance treatment efficacy and acceptability in the setting of recently acquired HCV infection (duration of infection <18 months). Within this second trial, a strategy of individualised response guided therapy was explored in which duration of therapy with PEG and RBV for acute and early chronic HCV infection was based on time to first undetectable HCV RNA, with total treatment duration ranging between 8-48 weeks. Eighty-two participants (HIV-positive 62%) were enrolled in ATAHC II (treated, n=52). SVR12 was 71% (37/52) with the majority (56%) receiving shortened therapy (8 or 16 weeks) with a combined SVR12 of 93% (unpublished data). SVR was associated with shorter treatment duration (OR 17.55; p=0.001) (unpublished data).

DARE-C I, a sub-study of ATAHC II, was established in 2013 to evaluate the safety and efficacy of response guided therapy with PEG, weight-based RBV and telaprevir (TVR) for recently acquired GT1 HCV infection (duration of infection 6-18 months). Treatment duration was dependent on time to first HCV RNA below the limit of detection and ranged between 8-24 weeks. Between April 2013 and May 2014, 14 participants

(79% HIV-positive) were enrolled. SVR12 by ITT was 71% (10/14) (unpublished data). By treatment duration, SVR12 was 71% (5/7) in those receiving PEG/RBV/TVR for 8 weeks, 100% (3/3) in those receiving PEG/RBV/TVR for 12 weeks and 100% (2/2) in those receiving PEG/RBV/TVR for 12 weeks + PEG/RBV for 12 weeks (24 weeks) (unpublished data). In those with HIV, SVR12 was 73% (8/11) (unpublished data).

DARE-C II is an ongoing pilot study exploring the safety, efficacy and feasibility of the dual interferon-sparing combination of SOF plus RBV in participants with recent HCV infection (duration of infection <12 months). The study is closed to recruitment. Results will be presented at the American Association for the Society of Liver Disease (AASLD) meeting in November 2015.

1.5 REACT rationale

Given the burden of HCV-related disease among PWID and HIV-positive MSM, strategies to enhance HCV assessment, treatment and prevention in these groups are urgently needed. Much of what is known about the timing of treatment initiation, regimen choice and duration of therapy in acute HCV infection comes from small observational studies and randomized controlled trials in selected populations with limited data on treatment in PWID and HIV co-infection. With recent rapid advances in HCV therapeutics, management strategies for acute HCV will evolve rapidly over the next few years.

The REACT study will compare the efficacy and safety of sofosbuvir/velpatasvir administered for 6 or 12 weeks in individuals with recent HCV infection. The role and activity of potent DAA regimens in acute HCV infection requires evaluation, with the potential to be given as highly efficacious, short course IFN-sparing regimens, maximising acceptability to patients, encouraging uptake of treatment, limiting further transmission and preventing progression to chronic liver disease.

2 Study objectives

2.1 Hypothesis

Six weeks treatment with sofosbuvir/velpastavir is non-inferior to twelve weeks treatment with sofosbuvir/velpastavir as assessed by sustained virological response at 12 weeks post treatment in the intention-to-treat population (SVR12).

2.2 Primary objective

The primary objective is to evaluate the proportion of patients with HCV RNA below the level of quantitation (target not detected [TND] or target detected, not quantifiable [TDnq]) at 12 weeks post end of treatment (SVR12) following sofosbuvir/velpatasvir therapy for 6 weeks (short treatment duration) as compared with 12 weeks (standard treatment duration) in people with recent HCV infection (duration of infection ≤12 months).

2.3 Secondary objective(s)

1 To evaluate the proportion of participants with HCV RNA below the level of quantitation (TND or TDnq) at the end of treatment (ETR), 4 weeks after treatment completion (SVR4) and 24 weeks after treatment completion (SVR24);

2 To evaluate the proportion of participants with undetectable HCV RNA through 2 years post treatment;

3 To evaluate the levels of adherence, factors associated with suboptimal adherence including HIV status, and the impact of suboptimal adherence on therapeutic response;

4 To evaluate the impact of treatment on illicit drug use, injecting behaviour and sexual risk taking behaviour (behavioural survey) during treatment;

5 To evaluate safety and tolerability

6 To evaluate the change in HIV RNA and CD4 (on-treatment and end of treatment);

7 To evaluate the rate and risk factors for reinfection during and up to 2 years following treatment;

8 To evaluate the immunological factors associated with treatment induced clearance and reinfection

9 To evaluate patient interest and attitudes towards long acting parenteral hepatitis C therapy (Long-Acting Hepatitis C Therapy Questionnaire)

3 Participant population

3.1 Number of Participants and Participant Selection

A total of 250 participants with recent HCV infection will be enrolled from drug and alcohol clinics, tertiary liver and infectious diseases clinics and community health centres across Australia, Canada, Germany, New Zealand, Switzerland, The Netherlands, the United Kingdom and the United States. The Kirby Institute may close or suspend screening prior to reaching 250 participants in order to manage the total study enrolment numbers.

The number of participants with HCV/HIV coinfection enrolled to the study will be capped at 70% (or less than 175 participants) of the total study population. In addition, the number of participants with HCV reinfection enrolled to the study will be capped at 50% (or less than 125 participants) of the total study population.

Selection of participants:

Enrolment into the study is at clinician discretion providing participant satisfies all eligibility criteria. However, the following situations should be considered prior to enrolment:

1. It is possible that participants presenting with acute HCV infection may spontaneously clear if followed untreated. Clinicians should consider it unlikely that the patient will spontaneously clear based on viral

load fluctuation before enrolling in this treatment study. It is suggested that a minimum of 4 weeks is observed from presentation to exclude this possibility.

2. Acute participants with very high viral loads (>7 log IU/ml) may be at higher risk of treatment failure. It is suggested to observe these patients until HCV viral load reduces to <7 log IU/ml before enrolling in study.

3.2 Inclusion criteria

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

1 Participants have voluntarily signed the informed consent form.
2 18 years of age or older.
3 Detectable HCV RNA at screening (>10,000 IU/ml), and in the opinion of the investigator is unlikely to demonstrate spontaneous viral clearance
4 HCV genotypes 1-6.
5 HBsAg negative
6 Negative pregnancy test at screening and baseline (females of childbearing potential only).
7 Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception
8 Medically stable on the basis of physical examination, medical history and vital signs
9 Adequate literacy to provide reliable responses to the study questionnaires
10 All fertile males and females must be using effective contraception during treatment and during the 30 days after treatment end.
11 Recently acquired HCV infection (estimated duration of infection ≤12 months)*

Recently acquired HCV infection as defined by:

A)

i) First anti-HCV Ab or HCV RNA positive within the previous 6 months

and

ii) Documented anti-HCV Ab negative within the 12 months prior to anti-HCV antibody positive result

OR

B)

i) First anti-HCV Ab or HCV RNA positive within the previous 6 months

and

ii) Acute clinical hepatitis (jaundice or ALT> 10 X ULN) within the previous 6 months prior to first positive HCV antibody or HCV RNA, with no other cause of acute hepatitis identifiable

OR

C) For cases of recent HCV reinfection the following criteria are required:

i) Documented prior HCV antibody positive with HCV RNA negative on at least 2 occasions 6 months apart *and*

ii) new HCV RNA positive within the previous 6 months

*Estimated duration of infection based on midpoint between last antibody negative or HCV RNA and first antibody positive or HCV RNA in the case of seroconversion and 6 weeks prior to date of maximum ALT in the case of acute hepatitis.

See Section 3.4 for 'Definitions used to calculate Estimated Date of Infection'.

If co-infection with HIV is documented, the subject must meet the following criteria:

1. Antiretroviral (ARV) untreated for >8 weeks preceding screening visit with CD4 T cell count >500 cells/mm^3
   OR
2. On a stable ARV regimen for >8 weeks prior to screening visit, with CD4 T cell count >200 cells/mm^3 and an undetectable plasma HIV RNA level.

- Suitable ARV include:
  - Nucleos(t)ide reverse transcriptase inhibitors: Tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), emtricitabine (FTC)Non-nucleoside reverse transcriptase inhibitors: Rilpivirine
  - Protease inhibitors: Atazanavir, darunavir, lopinavir, ritonavir
  - Integrase inhibitors: Dolutegravir, raltegravir, elvitegravir/cobicistat
- Contraindicated ARV include:
  - Efavirenz
    - 50% reduction in velpatasvir (GS-5816) exposure
  - Didanosine
  - Zidovudine
  - Tipranavir

Other ARV agents may be permissible at the time of study commencement pending further drug-drug interaction studies; please discuss with the Medical Monitor.

3.3 Exclusion criteria

Subjects 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. History of chronic pulmonary disease associated with functional limitation, severe cardiac disease, major organ transplantation or other evidence of severe illness, malignancy, or any other conditions which would make the patient, in the opinion of the investigator, unsuitable for the study

c. Solid organ transplant
d. Malignancy within 5 years prior to screening, with exception of specific cancers that may have been cured by surgical resection (basal cell skin cancer, etc.). Subjects under evaluation for possible malignancy are also excluded.
e. Significant drug allergy (such as anaphylaxis or hepatotoxicity).

2. Subject has a known or documented prior history of cirrhosis.
3. Subject shows evidence of significant liver disease in addition to hepatitis C, which may include but is not limited to drug- or alcohol-related cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson's disease, non-alcoholic steatohepatitis (NASH), or primary biliary cirrhosis
4 Any of the following lab parameters at screening:
    a. Direct bilirubin > 1.5 x ULN
    b. Platelets < 50,000/µL
    c. Creatinine clearance (CL_{cr}) < 50 mL/min
    d. Haemoglobin < 10 g/dL
    e. Albumin < 30g/L
    f. International Normalised Ratio (INR) >1.5 (unless subject is on a stable anticoagulant regimen or has known coagulopathy)
5. Pregnant or nursing female.
6. Use of prohibited concomitant medications as described in section 5.2
7. Chronic use of systemically administered immunosuppressive agents (e.g. prednisone equivalent > 10 mg/day)
8. Known hypersensitivity to velpatasvir, sofosbuvir or formulation excipients.
9. 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.
10. Any investigational drug ≤6 weeks prior to the first dose of study drug.
11. Previous failure of therapy with sofosbuvir or an NS5A inhibitor prior to the first dose of study drug.
12. Ongoing severe psychiatric disease as judged by the treating physician.
13. Frequent injecting drug use that is judged by the treating physician to compromise treatment safety.
14. Inability or unwillingness to provide informed consent or abide by the requirements of the study.
15. Prior enrolment within this study.

Subjects will be stratified by genotype/subtype, HIV status and primary or reinfection for analysis.

3.4 Definitions used to calculate Estimated Date of Infection

The estimated date of HCV infection will be determined using data obtained at the screening visit according to the following rules (**Table 1**):

Table 1. Estimated duration of infection calculation rules

Category	Estimated date of HCV infection
Acute clinical HCV	6 weeks prior to onset of acute clinical symptoms
Acute asymptomatic HCV ALT < 400 IU/L	Mid-point between last negative HCV antibody or HCV RNA and first positive HCV antibody or HCV RNA
Acute asymptomatic HCV ALT > 400 IU/L	6 weeks prior to the date of peak ALT unless the estimated date of infection is after the date of first HCV antibody positive test. Then, 6 weeks prior to the date of the first HCV antibody positive test
HCV antibody negative and HCV RNA positive at screening	6 weeks prior to the screening date

The estimated date of HCV will then be used to determine the estimated duration of HCV infection.

4 Study design

4.1 Summary of study design

This study will be conducted as a phase III randomised, open-label, non-inferiority multicentre international trial.

A total of 250 people with recently acquired hepatitis C will be enrolled and randomised.

The number of participants with HCV/HIV coinfection enrolled to the study will be capped at 70% (or less than 175 participants) of the total study population. In addition, the number of participants with HCV reinfection enrolled to the study will be capped at 20% (or less than 50 participants) of the total study population.

The study consists of a screening phase (-12 to -4 weeks), treatment commencement from baseline, randomisation between week 5 and 6, treatment for another 6 weeks for those randomised to standard therapy (12 weeks of treatment) or end of treatment for those randomised to shortened treatment (6 weeks of treatment). All participants will then enter the follow-up phase (96 weeks) to evaluate treatment response and reinfection (Figure 1). Randomisation will be using blocks and will be stratified by study site and HIV status.

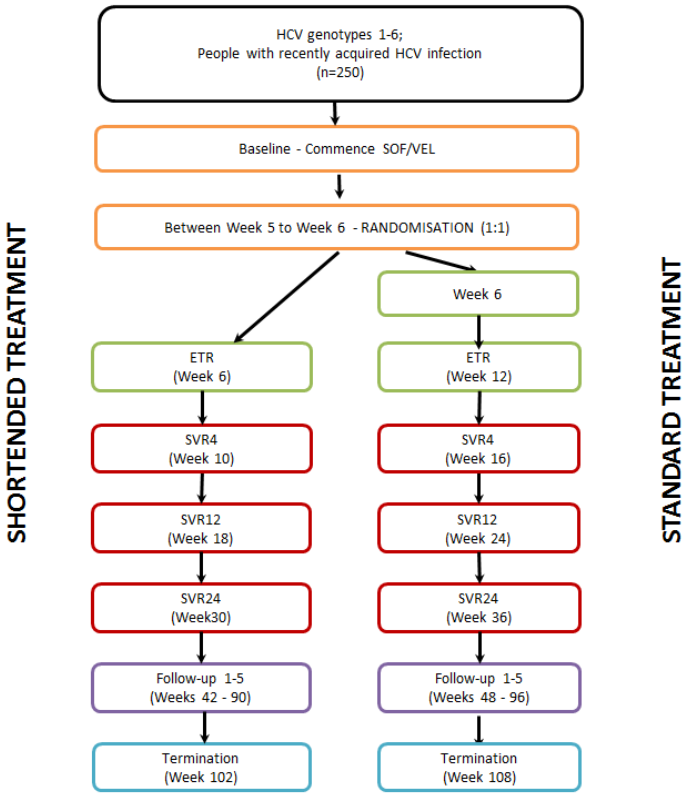

Figure 1: Study Schema

Participants who become re-viraemic following an end of treatment response will be followed monthly for six months. After completing the monthly follow-up visits, participants will continue to attend three monthly follow-up visits up to two years. Please see section 7 'Reinfection follow-up' for more details.

4.2 Visit Schedule

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

Screening assessments must be completed within in 12 weeks prior to baseline. There must be a minimum of 4 weeks between screening and baseline.

Following screening, eligible participants will commence treatment. Between week 5 and week 6 of treatment, the participants will be randomised to either the shortened or standard treatment duration. On-treatment visits will be conducted at weeks 1, 2, 4 and 6 (end of treatment for participants on shortened treatment duration), weeks 8 and 10 (for participants on standard treatment duration only). Participants on standard treatment duration will attend end of treatment at week 12. For participants randomised to shortened treatment, follow-up visits will be conducted at week 10 (SVR4), week 18 (SVR12), week 30 (SVR24), week 42 (FU1), week 54 (FU2), week 66 (FU3), week 78 (FU4), week 90 (FU5) and week 102 (Termination). For participants randomised to standard treatment, follow-up visits will be conducted at week 16 (SVR4), week 24 (SVR12), week 36 (SVR24), week 48 (FU1), week 60 (FU2), week 72 (FU3), week 84 (FU4), week 96 (FU5) and week 108 (Termination).

4.3 Treatment Discontinuation Criteria

Study drug must be discontinued in the following instances:

- Unacceptable toxicity
- Pregnancy of female subject
- Significant protocol violation
- Participant request to discontinue 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

Participants who cease study medication will, wherever possible, continue to be followed up according to the protocol study plan. Participants may revoke consent for follow-up without jeopardizing their relationship with either their doctor or the UNSW. If a participant revokes consent then, if possible, all assessments scheduled for the final visit should be completed.

5 Treatment of participants

5.1 Sofosbuvir/velpatasvir dosage and administration

Participants will receive six or twelve weeks of open-label sofosbuvir/velpatasvir (400mg/100mg daily) in an oral once-daily fixed dose combination. Dose modifications are prohibited.

5.2 Study Drug Adherence and Drug Accountability

Therapy will be administered in two-weekly supply. Participants will be asked to return study medication every two weeks. Study drug will be reconciled using a pill count on all returned drug bottles.

Participants will also be required to complete an adherence questionnaire as described in section 6.2.

5.3 Prior and Concomitant Medications

Concomitant medication must be recorded in the source documents and eCRF from screening until the last dose of study medication.

The following medications are prohibited from **six weeks prior to the baseline visit** through to the end of treatment:

- Haemotologic stimulating agents (e.g. erythropoiesis-stimulating agents [ESAs]; granulocyte colony stimulating factor [GCSF]; thrombopoietin [TPO] mimetics)
- Chronic systemic immunosuppressant use including, but not limited to corticosteroids (prednisone equivalent of >10 mg/day for >2 weeks), azathioprine, or monoclonal antibodies (e.g. infliximab)

- Investigational agents or devices for any indication
- Drugs disallowed per prescribing information of SOF

Concomitant use of certain medications or herbal/natural supplements (inhibitors or inducers of drug transporters i.e. P-gp) with study drug may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drug or these medications.

Due to decreases in sofosbuvir or velpatasvir exposure, use of sofosbuvir/velpatasvir with potent P-gp and moderate or potent CYP inducers is not recommended (83-85).

The use of the ”Disallowed” agents in **Table 2** is prohibited from 21 days prior to Baseline through to the end of treatment except Amiodarone which is prohibited from 60 days prior to Baseline through to the end of treatment.

Examples of representative medication which are prohibited or are used with caution are listed below:

Table 2: List of Disallowed Medications

Drug Class	Agents Disallowed	Use with Caution
Acid Reducing Agents[a]		H2-Receptor Antagonists[a], Antacids[a] , Proton Pump Inhibitors[a]
Anticonvulsants[b]	Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin,	
Antimycobacterials[b]	Rifabutin, Rifapentine, Rifampin	
Antiretrovirals	Efavirenz [b]	
Cardiac Medications[c]	Amiodarone[e],	Bosentan, Digoxin[c], Diltiazem, Dronedarone, Olmesartan, Quinidine, Ranolazine, Telmisartan, Valsartan, Verapamil
Herbal/Natural Supplements[b]	St. John's Wort, Echinaccea, Milk Thistle (i.e. silymarin), Chinese herb Sho-Saiko-To (or Xiao-Shai-Hu-Tang)	
HMG-CoA Reductase Inhibitors[d]		Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin (≤10 mg/day), Simvastatin
Other	Modafinil[b], sulfasalazine[c], methotrexate[c]	

[a] H2-receptor Antagonists must not exceed a dose of 20 mg famotidine or equivalent and can be taken simultaneously with SOF/VEL and/or staggered by 12 hours. Antacids that directly neutralize stomach acid (i.e. Tums, Maalox) may not be taken within 4 hours (before or after) of SOF/VEL administration. Proton Pump Inhibitors equivalent to omeprazole 20 mg can be taken simultaneously with SOF/VEL in the fed state.

[b] May result in a decrease in the concentration of study drugs

[c] May result in an increase in the concentration of study drugs and/or concomitant medications; monitor for signs and symptoms of digoxin toxicity

[d] Use with SOF/VEL may result in an increase in the concentration of HMG-CoA Reductase Inhibitors. Monitor for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis.

[e] 60 day washout period applies.

Refer to http://www.hep-druginteractions.org/ and product information for further data.

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

6 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	body weight[a], height[a]
Biochemistry	Creatinine, glucose, sodium, chloride, and potassium, creatine kinase
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
HCV RNA	Must be quantitative at Screening
HCV Genotype	Within 12 months prior to screening
HAV Serology	Hepatitis A total Ab (IgG), Hepatitis A IgM
HBV Serology	Anti-HBc, HBsAg
HCG Pregnancy Test	For women of childbearing potential, a negative urine (or serum) HCG test at screening and baseline
Questionnaires	Behavioural survey, abbreviated behavioural survey, adherence questionnaire, Health Outcomes Survey (EQ-5D), Long-Acting Hepatitis C Therapy Questionnaire

[a] at screening only

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

Initial screening period (Week -12 to Week -4)

- Informed consent
- Medical history
- FibroScan®
- Vital signs and physical examination
- HCV antibody
- HCV RNA and genotype (Local laboratory)
- LFTs, FBC and biochemistry
- Clotting - INR
- HIV antibody, HAV & HBV serology
- CD4/CD8 & HIV viral load (HIV positive participants only)
- Pregnancy test (females of child bearing potential only)
- Study behavioural questionnaire
- Concomitant medication
- Health outcomes survey (EQ-5D)
- Research specimen collection (EDTA plasma, whole blood & ACD Plasma/PBMCs)

Baseline visit (Week 0)

- Vital signs and physical examination
- HCV RNA (Local laboratory)
- LFTs, FBC and biochemistry
- Pregnancy test (females of child bearing potential only)
- Adverse Events
- Concomitant medication
- Abbreviated Behavioural questionnaire
- Long-Acting Hepatitis C Therapy Questionnaire*
- Research specimen collection (EDTA plasma, whole blood & ACD Plasma/PBMCs)

* The Long-Acting Hepatitis C Therapy Questionnaire aims to obtain participant interest and attitudes towards long-acting parenteral hepatitis C therapy. All currently enrolled participants will complete the Long-Acting Hepatitis C Therapy Questionnaire at their next scheduled visit.

Week 1 (+/- 3 days)

- LFTs, FBC and biochemistry
- Adverse Events
- Concomitant medication
- Research specimen (EDTA plasma & ACD Plasma/PBMCs)

Week 2 (+/- 3 days)

- LFTs, FBC and biochemistry
- Adherence questionnaire
- Adverse Events
- Concomitant medication
- Research specimen (EDTA plasma & ACD Plasma/PBMCs)
- SOF/VEL pill count

Week 4 (+/- 3 days)

- LFTs, FBC and biochemistry
- Pregnancy test (females of child bearing potential only)
- Adherence questionnaire
- Adverse Events
- Concomitant medication
- Research specimen (EDTA plasma & ACD Plasma/PBMCs)
- SOF/VEL pill count

Between Week 5 and Week 6 – RANDOMISATION

Week 6 (+/- 3 days)

For participants in the shortened treatment arm – complete the ETR visit.

For participants in the standard treatment arm complete the following assessments.

- LFTs, FBC and biochemistry
- Abbreviated Behavioural questionnaire
- Adherence questionnaire
- Adverse Events
- Concomitant medication
- Research specimen (EDTA plasma & ACD Plasma/PBMCs)
- SOF/VEL pill count

Week 8 (+/- 3 days) and Week 10 (+/- 3 days) – STANDARD DURATION ONLY

- LFTs, FBC and biochemistry
- Pregnancy test (females of child bearing potential only) – week 8 only
- Adherence questionnaire
- Adverse Events
- Concomitant medication
- Research specimen collection (EDTA plasma)
- SOF/VEL pill count

End of Treatment (ETR) – Week 6 (Shortened treatment) or Week 12 (Standard treatment) (+/-3 days)

- HCV RNA (Local laboratory)
- LFTs, FBC and biochemistry
- CD4/CD8 & HIV viral load (HIV positive participants only) – Standard treatment arm only
- Pregnancy test (females of child bearing potential only) – Standard arm treatment only
- Adverse Events
- Concomitant medication
- Abbreviated Behavioural questionnaire
- Adherence questionnaire
- Research specimen collection (EDTA plasma & ACD Plasma/PBMCs)
- SOF/VEL pill count

Post Treatment Follow-up Visits

Post Treatment Week 4 (SVR4) - Week 10 (Shortened treatment) or Week 16 (Standard treatment) (+/- 3 days)

- LFTs, FBC and biochemistry
- Pregnancy test (females of child bearing potential only)
- Adverse Events
- Research specimen collection (EDTA plasma & ACD Plasma/PBMCs *)

*To be collected in patients with suspected relapse/reinfection only

Post Treatment Week 12 (SVR12) - Week 18 (Shortened treatment) or Week 24 (Standard treatment) (+/- 14 days)

- FibroScan®
- HCV RNA (Local laboratory)
- LFTs, FBC and biochemistry
- CD4/CD8 & HIV viral load (HIV positive participants only)
- Abbreviated Behavioural questionnaire
- Health outcomes survey (EQ-5D)
- Research specimen collection (EDTA plasma & ACD Plasma/PBMCs *)

*To be collected in patients with suspected relapse/reinfection only

Post Treatment Week 24 (SVR24) - Week 30 (Shortened treatment) or Week 36 (Standard treatment) (+/- 14 days)

- FibroScan®
- HCV RNA (Local laboratory)
- LFTs
- CD4/CD8 & HIV viral load (HIV positive participants only)
- Abbreviated Behavioural questionnaire
- Research specimen collection (EDTA plasma & ACD Plasma/PBMCs *)

*To be collected in patients with suspected relapse/reinfection only

Post Treatment Weeks - 42 (FU1), 54 (FU2), 66 (FU3), 78 (FU4) and 90 (FU5) – Shortened treatment or
- 48 (FU1), 60 (FU2), 72 (FU3), 84 (FU4) and 96 (FU5) – Standard Treatment

(+/- 28 days)

- FibroScan®
- HCV RNA (Local laboratory)
- LFTs
- CD4/CD8 & HIV viral load (HIV positive participants only)
- Abbreviated Behavioural questionnaire
- Research specimen collection (EDTA plasma & ACD Plasma/PBMCs *)

*To be collected in patients with suspected relapse/reinfection only

Termination Visit - Week 102 – Shortened treatment or Week 108 – Standard treatment

- FibroScan®
- HCV RNA (Local laboratory)
- LFTs
- CD4/CD8 & HIV viral load (HIV positive participants only)
- Abbreviated Behavioural questionnaire
- Research specimen collection (EDTA plasma & ACD Plasma/PBMCs *)

*To be collected in patients with suspected relapse/reinfection only

Re-treatment

Any participant receiving re-treatment will have the following parameters collected:

- Re-treatment regimen, dose and duration
- Re-treatment outcome

6.2 Prevention of Pregnancy

6.2.1 Definitions of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential from menarche until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure. Women are considered to be in a post-menopausal state when they are > 54 years of age with cessation of previously occurring menses for > 12 months without an alternative cause. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

6.2.2 Female Participants

From screening onwards until 30 days after the last dose of SOF/VEL, a female participant and her partner must agree to use 2 effective methods of contraception when having sexual intercourse.

One method must be a non-hormonal barrier method that prevents transmission of fluids. Acceptable non-hormonal barrier methods include male condoms OR female condoms [female and male condoms are not to be used both simultaneously as friction between the two can result in damage or breakage of either product], diaphragm or cervical cap.

The other method must be hormonal. Acceptable hormonal contraceptives are the oral contraception pill, the hormonal implant, the hormonal injection, the hormonal IUD, the vaginal ring and the transdermal contraceptive patch. Other acceptable methods are tubal sterilisation or vasectomy in male partner.

Systemic hormonal contraceptives (i.e., the pill) should be effective in women taking SOF/VEL. No significant drug interactions were seen when systemic hormonal contraceptives and SOF or VEL were given to women.

6.2.3 Male Participants

For a male participant, they must agree not to get a woman pregnant during the study. A male participant who has a female partner of child-bearing potential must agree to use 2 effective methods of contraception. From screening through 30 days after the last dose of SOF/VEL, both the male participant and his female partner should use a male condom in combination with another effective method, such as, intrauterine device, diaphragm with spermicidal jelly or cervical cap with spermicidal jelly.

The male participant must agree to inform his sexual partner that he is participating in a research study which requires his partner and him to use 2 methods of contraception.

6.3 Study Questionnaires

All subjects will undertake a number of study questionnaires at screening, baseline, and selected follow-up visits.

The Behavioral Questionnaire

The study staff will assist participants to complete this questionnaire. The behavioural survey will collect information on the following:

- Demographics
- HIV and drug treatment history
- Drug and alcohol usage
- Injecting risk behaviours
- Sexual risk behaviours
- Treatment acceptance and willingness (prior to treatment commencement only)
- Attitudes and behaviours associated with HCV reinfection

An abbreviated behavioural questionnaire (follow-up) will be administered at subsequent time points during the study.

Adherence Survey

Adherence to SOF/VEL will be assessed by two-weekly structured self-report adherence questionnaire and two-weekly pill count.

Health Outcomes Survey (EQ-5D)

The EQ-5D health outcome 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.

Long-Acting Hepatitis C Therapy Questionnaire

The Long-Acting Hepatitis C Therapy Questionnaire aims to obtain participant interest and attitudes towards long-acting parenteral hepatitis C therapy. The questionnaire collects information on the following topics;

- Receiving an injection for hepatitis C therapy
- Receiving an implant for hepatitis C therapy
- Receiving an expanding long acting pill for hepatitis C therapy
- Current and past medication use

7 Reinfection follow-up

All participants in this study will be followed up to two years for reinfection with three monthly visits. Participants who become re-viraemic following an end of treatment response will be followed monthly for six months as per 7.1 Schedule of Assessments - Reinfection. After completing the monthly reinfection follow-up visits, participants will continue to attend three monthly standard follow-up visits up to two years as per the main study Schedule of Assessments.

Please see the following section 7.1 ‘Schedule of Assessments – reinfection’ for study visits and assessments.

7.1 Schedule of Assessments – Reinfection

Assessment/Procedure	Reinfection monthly follow-up visits						Continue 3 monthly FU - Refer to Arm A or Arm B Schedule of Assessments
Reinfection visit number	**RFU1**	**RFU2**	**RFU3**	**RFU4**	**RFU5**	**RFU6**	
Visit Window (Days)	**+/- 3**	**+/- 3**	**+/- 3**	**+/- 3**	**+/- 3**	**+/- 3**	
HCV-RNA testing (local lab.)	x	x	x	x	x	x	
Liver function tests	x	x	x	x	x	x	
Behavioural questionnaire	x		x			x	
Research Specimen Collection							
EDTA plasma (10ml)	x	x	x	x	x	x	
ACD Plasma/PBMCs (60ml)	x	x	x	x	x	x	

8 Recording and reporting Adverse Events (AEs)

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

8.1.1 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. All such events will be recorded at each study visit on the adverse event case report form.

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 4 weeks after drug discontinuation must be reported on the Adverse Event Page of the case report form (CRF).

Laboratory test abnormalities 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 without clinical sequelae should not be reported as an adverse event.

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

The definition of a SAE is any untoward medical occurrence that at any dose:

1) Results in death
2) Is life-threatening
   (Note: the term "life-threatening" in the definition of "serious" refers to an event/reaction in which the participant was at risk of death at the time of event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
3) Requires in-patient hospitalisation or prolongation of existing hospitalisation
4) Results in persistent or significant disability/incapacity
5) Results in a congenital anomaly/birth defect
6) Results in a medically important event or reaction (includes infections from contaminated medicinal product/s)

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the participant or may require intervention to prevent one of the outcomes listed in the definition above.

8.1.3 Special Situation Report (SSR)

Special Situation Reports are defined as:

a) Pregnancy Reports
b) Reports of Medication Abuse, Error, Misuse, Off-label Use or Overdose
c) Lack of Effect Reports
d) Reports of AEs in infants following exposure from breastfeeding
e) Reports of AEs associated with Product Complaints or arising from Occupational Exposure

8.2 Assessment of Adverse Events and Serious Adverse Events

8.2.1 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

8.2.2 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

8.3 Reporting Requirements

8.3.1 Adverse Events

All adverse events from the date of signing the consent form until four weeks after the last dose of study drug administration should be reported on the case report form.

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.

8.3.2 Serious Adverse Events

All serious adverse events (SAEs) should be reported within 24 hours to the Kirby Institute and Gilead DPSH by email or fax on the Serious Adverse Event Reporting Form. 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 ONE WORKING DAY 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).

All SAEs must be reported in English and be submitted to **BOTH the Kirby Institute AND Gilead:**

Kirby Institute:	Email:	reactvh@kirby.unsw.edu.au
	Fax:	+61 2 9385-9214.
Gilead DSPH:	Email:	Safety_FC@gilead.com
	Fax:	+1 650-522-5477

8.3.3 Special Situation Reports

All SSRs must be reported in English using the SAE Reporting Form and submitted to **BOTH the Kirby Institute AND Gilead** within 15 calendar days of first becoming aware of any such safety information and in accordance with applicable laws, rules, regulations and guidance**:**

Kirby Institute:	Email:	reactvh@kirby.unsw.edu.au
	Fax:	+61 2 9385-9214
Gilead DSPH:	Email:	Safety_FC@gilead.com
	Fax:	+1 650-522-5477

8.3.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

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.

9 Packaging, labeling, storage and accountability of clinical trial supplies

All study drugs will be provided by Gilead Sciences, Inc and should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist.

Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects.

A designated person at the study site must receive clinical trial supplies. That person must check that the supplies are in good condition and are complete as per the shipping records. Drugs must be stored in a secure location with limited access. Clinical trial supplies 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. Participants will be instructed to return all study drug containers (including empty ones) to the site staff during the course of the study and all containers must be retained for review by the sponsor's monitor until the end of the study.

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

9.1 Formulation

The SOF/VEL (400mg/100mg) tablets are pink, diamond shaped, film-coated tablets, debossed with "GSI" on one side and "7916" on the other side. In addition to the active ingredient, SOF/VEL tables also contain the following inactive ingredients: copovidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and iron oxide red.

9.2 Packaging and Labelling

SOF/VEL 400mg/100mg tablets are packaged in bottles of 14 tablets.

9.3 Storage and handling

SOF/VEL should be stored at controlled room temperature until required for administration. Controlled room temperature is defined at 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F to 86°F).

Subjects should be counselled to store SOF/VEL at room temperature not in the refrigerator.

All drug products should be stored in a securely locked area, assessable 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.

9.4 Dosage and administration

SOF/VEL is to be administered once daily with or without food. Each subject must be given instructions to maintain approximately the same daily dosing interval between study drug doses. Subjects should be instructed to swallow the study medication tablet whole. Subjects should be instructed to only remove the tablet immediately prior to dosing.

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

10 Biological samples

10.1 Laboratory supplies and sample processing

Laboratory supplies for collection of research specimens (plasma, whole blood and) will be supplied by the Kirby Institute.
The following blood samples will be collected as time point specified in the schedule of assessments:

1. 10 mL EDTA plasma for HCV RNA testing and future HCV related research (20ml at screening and baseline);
2. 4mL Whole Blood for human genomic DNA analysis collected from the screening and baseline EDTA plasma samples;
3. 60 ml ACD plasma / PBMCs

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. Viral sequences may also be used to distinguish relapse from reinfection, to examine the prevalence of mixed infection, to look at the prevalence and emergence of resistance associated variants (RAVs) and for phylogenetic analysis. EDTA plasma may also be used for drug level monitoring.

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.

10.2 Shipping of biological samples

Samples must only be shipped to the Kirby Institute laboratory on the instruction from the Study 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.

10.3 Future use of biological samples

After the samples have been analysed 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. Subjects not wishing to have their samples stored or used in future hepatitis C related research will not be eligible to participate in this study.

11 Statistics

11.1 Sample size

The primary objective of this trial is to establish the non-inferiority of short duration treatment (6 weeks) to the standard duration treatment (12 weeks).

Assuming an expected SVR of 90% in the control arm, 113 participants per arm will be required to give 80% chance that the two sided confidence interval of the difference between regimens has a lower limit greater than -12**%.**

A total of 250 subjects enrolled and randomised will comprise the intention-to-treat (ITT) population and will form the study population for evaluation of the primary and secondary endpoints.

11.2 Assessments of Safety and Efficacy

The primary analysis will summarise study variables when the last patient recruited has completed 12 weeks follow-up post treatment. This analysis will be reviewed by the Protocol Steering Committee and then presented publicly. Subsequent analyses will be performed up until and at time that the last patient has completed study follow up (or discontinued from the study).

This is a multicentre, randomised study aiming to demonstrate non-inferiority of a 6 week as compared with a 12 week course of sofosbuvir/velpatasvir for recent HCV infection.

Primary endpoint:
The primary endpoint is the proportion of participants with HCV RNA below the level of quantitation (target not detected [TND] or target detected, not quantifiable [TDnq]) at 12 weeks post end of treatment (SVR12)
Secondary endpoints:

- Secondary virological endpoints
    - The proportion of participants with:
        - ETR defined as HCV RNA below the level of quantitation at end of therapy
        - SVR 4 defined as HCV RNA below the level of quantitation 4 weeks post therapy
        - SVR 24 defined as HCV RNA below the level of quantitation 24 weeks post therapy
        - HCV RNA below the level of quantitation through 2 years post treatment

      Results will be stratified by HCV genotype and HIV-coinfection.
- 80/80 adherence: Defined as the receipt of >80% of scheduled doses for >80% of the scheduled treatment period.
- 90/90 adherence: Defined as the receipt of >90% of scheduled doses for >90% of the scheduled treatment period.
- 100/100 adherence: Defined as the receipt of 100% of scheduled doses for 100% of the scheduled treatment period.
- On-treatment adherence: Calculated by subtracting the number of missed doses from the total number of doses of scheduled treatment and dividing by the total intended therapy duration. This measures the proportion of doses received from the time that treatment was initiated until treatment was discontinued or completed.
- Toxicity: Proportion of participants with at least one severe or potentially life threatening (grade 3 or 4) adverse event.
- Early treatment discontinuation: Discontinuation of therapy prior to the per-protocol planned end of treatment (6 or 12 weeks depending on study arm).
- Resistance associated variants (RAVs): The proportion of treated subjects with development of RAVs following virological relapse or breakthrough.
- Reinfection rate: Rates of HCV reinfection will be calculated using person-time of observation during and up to 48 months following end of treatment.
- Baseline characteristics, on-treatment adherence, risk behaviours and toxicity will be evaluated among subjects withdrawing prior to randomisation.

11.3 Analyses

Efficacy analyses:
There will be one primary pair-wise comparison of the efficacy endpoints: shortened duration therapy versus standard duration therapy. Comparisons will be simple, direct two-sample comparisons of randomised treatment groups unadjusted for baseline covariates. If there is evidence of substantial imbalance at baseline in important covariates, further adjusted analyses will also be performed. If any randomisation mistakes occur, such that patients incorrectly receive the wrong treatment, then key efficacy endpoints will be performed where these patients will be excluded.

The primary analysis will compare randomised treatment groups on an ITT basis including all available data. The primary endpoint, SVR12, will be calculated for each patient based on all available data. Treatment arms will be regarded as non-inferior if the difference in proportion between regimens has a lower limit greater than -12**%.** Secondary analyses will compare randomised treatment groups based on available data (per protocol).

Proportions and 95% confidence intervals will be reported for both the primary and secondary virological endpoints. These will be provided overall, by treatment duration, by HCV genotype and by HIV status, and will be assessed for both the ITT and PP populations.

SVR 4, SVR 12 and SVR 24 rates will be compared to SVR rates demonstrated in historical controls in the ATAHC I, ATAHC II, DARE-C I and DARE-C II studies. Differences in proportions between studies will be summarised as n (%) in each group, with percent difference between cohorts with 95% confidence interval.

Factors associated with ITT study population treatment efficacy will be evaluated by univariate analysis, and will include, but are not limited to, the following variables: socio-demographic factors (age, gender, ethnicity); virological factors (baseline HCV viral load, HCV genotype); risk behaviors (injecting drug use, sexual behaviour); and HIV co-infection.

Additional treatment efficacy evaluations will be conducted among the *per protocol study population*, defined as subjects who receive >80% of planned treatment.

The impact of 80/80 adherence, 90/90 adherence, 100/100 adherence, on-treatment adherence and early discontinuation on SVR will also be evaluated.

To assess HCV reinfection, among people with virological suppression, participants with HCV RNA recurrence (detectable HCV RNA following HCV virological suppression) will be identified. HCV RNA sequencing will be performed on the first available detectable HCV RNA sample and the first available detectable HCV RNA sample following HCV RNA recurrence. HCV reinfection will be defined by the detection of infection with an HCV strain which was distinct from the primary infecting strain based on previously defined genetic distance-based cut-offs for HCV reinfection and HCV viral relapse(72), patristic distance-based cut-offs and phylogenetic tree construction (86). Rates of HCV reinfection will be calculated using person-time of observation up to 48 months following the end of treatment. Modified intention-to-treat analyses will also be performed in which individuals with confirmed reinfection are removed from the efficacy analysis.

Immunological and virological assays will also be performed to assess the impact of HCV treatment on immune responses during treatment.

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

12 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. All DSMB members will be independent of the study and the Kirby Institute. The meeting will include the interim efficacy and safety analysis which will be performed when the first 50 subjects in each arm have either received treatment and completed 12 weeks of follow-up post treatment (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.

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.

13 Data collection, source documents and record retention

13.1 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 two source data verification visits during the study. These should occur shortly after enrolment of the first participant(s) and following completion of all study visits.

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.

13.2 Linkage of data - Applicable to Australian Sites Only

At a later date, the study data may be linked with public registries such as the National Notifiable Diseases Database, hospital morbidity databases, cancer and death registries and future research databases.

13.3 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.

14 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).

15 Confidentiality of data

15.1 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. The following wording may be included in the protocol.

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.

15.2 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.

16 Governance

The study is sponsored by UNSW and coordinated through the Kirby Institute for infection and immunity in society. It is funded by the University of New South Wales (UNSW) and Gilead Sciences Inc. The study drugs will be provided by Gilead Sciences Inc. The Kirby Institute has established governance and implementation structures which use resources efficiently to deliver program objectives on schedule.

17 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.

18 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.

19 List of References

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20 Abbreviations List

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
DAA	Direct Acting Antiviral
End of treatment	Date of last dose of treatment
ETR	End of Treatment Response, undetectable HCV RNA at the completion of treatment
FBC	Full Blood Count (haemoglobin, WCC including differentials, platelets)
HCV	Hepatitis C Virus
HCV RNA re-viraemia	Detection of the hepatitis C virus again following an end of treatment response
HIV	Human Immunodeficiency Virus
IDUs	Injection Drug Users
INR	International Normalized Ratio
LFTs	Liver Function Tests – albumin, ALT, AST, alkaline phosphatase, GGT, total bilirubin, total protein
LLOQ	Lower Limit Of Quantification
GGT	Gamma Glutamic Transpeptidase
Hgb	Haemoglobin
PEG-IFN	Pegylated interferon alfa 2a
PWID	People Who Inject Drugs
Superinfection	Detection of infection with an HCV strain which was distinct from the primary infecting strain in those with HCV virological persistence
Reinfection	Detection of infection with an HCV strain which was distinct from the primary infecting strain among participants with either spontaneous or treatment-induced HCV virological suppression (≤15 IU/ml on Roche TaqMan).
RAV	Resistance-associated variants
RVR	Rapid Virological Response, HCV RNA undetectable at week 4 of treatment
vRVR	Very Rapid Virological Response, HCV RNA undetectable at week 2 of treatment
SOF	Sofosbuvir
SVR4	Sustained Virological Response, HCV RNA undetectable 4 weeks post-treatment
SVR12	Sustained Virological Response, HCV RNA undetectable 12 weeks post-treatment
SVR24	Sustained Virological Response, HCV RNA undetectable 24 weeks post-treatment
TND	Target not detected (HCV RNA below the level of quantitation)
TDnq	Target detected, not quantifiable (HCV RNA detected but not quantifiable)
Undetectable HCV RNA	HCV RNA results that are <15 IU/ml (non-quantifiable), but “detectable” will be considered as undetectable HCV RNA
VEL	Velpatasvir
WCC	White Cell Count