REACT

STATISTICAL ANALYSIS PLAN

A randomised study of interferon-free treatment for recently acquired hepatitis C in people who inject drugs and people with HIV co-infection

Study Title:	A randomised study of interferon-free treatment for recently acquired hepatitis C in people who inject drugs and people with HIV co-infection
Name of Study Drug:	sofosbuvir/velpatasvir
Protocol Number:	VHCRP1401
Protocol Version:	5.0
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Co-ordinating Principal Investigators:	A/Professor Gail Matthews
Name/s of Sponsor:	UNSW Sydney
Analysis Type:	Primary – SVR12
Analysis Plan Version:	Final V1.0
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Analysis Plan Author:	Kathy Petoumenos

Contents

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
APRI	AST:platelet ratio index
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BLoQ	below the lower limit of quantitation
CI	confidence interval
CPT	Child-Pugh-Turcotte
DAA	direct acting antiviral
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FDC	fixed-dose combination
FU	follow-up
GT	genotype
HCV	hepatitis C virus
HLGT	high level group term
HLT	high level term
INR	international normalized ratio of prothrombin time
LLOQ	lower limit of quantitation
LLT	lower level term
LSM	liver stiffness measurement
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
PT	preferred term
Q1	first quartile
Q3	third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SVR	sustained virologic response
SVRx	sustained virologic response x weeks after stopping study drug
TD	target detected
TND	target not detected
ULN	upper limit of normal

STUDY DEFINITIONS

HCV virological suppression is defined as HCV RNA below the lower limit of quantitation (LLoQ) (target not detected [TND] or target detected, not quantifiable [TDnq]).

An *end-of-treatment response (ETR)* is defined as plasma HCV RNA below the LLoQ (TND or TDnq) at the end of treatment.

Sustained virological response at 4 weeks post-treatment (SVR4) is defined as plasma HCV RNA below the LLoQ (TND or TDnq) at 4 weeks post cessation of treatment.

Sustained virological response at 12 weeks post-treatment (SVR12) is defined as plasma HCV RNA below the LLoQ (TND or TDnq) at 12 weeks post cessation of treatment.

Sustained virological response at 24 weeks post-treatment (SVR24) is defined as plasma HCV RNA below the LLoQ (TND or TDnq) at 24 weeks post cessation of treatment.

HCV virologic failure is defined as *non-response* (failure of virological suppression on-treatment with quantifiable HCV RNA at all time points between baseline and end of treatment)

Reinfection is defined by the presence of quantifiable HCV RNA after an ETR and detection of infection with an HCV strain that was distinct from the primary infecting strain (heterologous virus on sequencing of Core-E2 and/or NS5B regions).

Relapse is defined by recurrent viraemia by SVR12 where reinfection is not confirmed.

The *presentation of recent HCV infection* at the time of diagnosis is classified as either *acute clinical* or *asymptomatic infection*. *Acute clinical infection* includes participants with a documented clinical history of symptomatic seroconversion illness (including, but not limited to, the presence of jaundice, nausea/vomiting, abdominal pain, fever and hepatomegaly) and those without clinical symptoms but with a documented peak ALT >10 times the upper limit of normal (ULN) within the 12 months prior to diagnosis. *Asymptomatic infection* includes participants with anti-HCV antibody seroconversion but no acute clinical symptoms or documented peak ALT <10x ULN.

The *duration of HCV infection* at screening and baseline will be calculated from the estimated date of infection. *The estimated date of clinical infection* is calculated as six weeks before onset of seroconversion illness or six weeks before the first ALT >10x ULN. The *estimated date of asymptomatic infection* is calculated as the midpoint between the last negative anti-HCV antibody or HCV RNA and the first positive anti-HCV antibody or HCV RNA. For participants who were anti-HCV antibody negative and HCV-RNA positive at screening, the estimated date of infection is six weeks before enrolment, regardless of symptom status.

On-treatment adherence will be calculated by subtracting the number of missed doses from the total number of doses prescribed for therapy duration and dividing by the total number of doses prescribed for therapy duration. By pill count and self-reported questionnaire, compliance with sofosbuvir/velpatasvir will be individually calculated at the 80, 90 and 100 adherence levels, defined as receipt of ≥80, ≥90 or 100% of scheduled doses.

STUDY DESIGN AND OBJECTIVES

Study Objectives

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

- 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);
- To evaluate the proportion of participants with undetectable HCV RNA through 2 years post treatment;
- To evaluate the levels of adherence, factors associated with suboptimal adherence including HIV status, and the impact of suboptimal adherence on therapeutic response;
- To evaluate the impact of treatment on illicit drug use, injecting behaviour and sexual risk taking behaviour (behavioural survey) during treatment;
- To evaluate safety and tolerability;
- To evaluate the change in HIV RNA and CD4 (on-treatment and end of treatment);
- To evaluate the rate and risk factors for reinfection during and up to 2 years following treatment;
- To evaluate the immunological factors associated with treatment induced clearance and reinfection;
- To evaluate patient interest and attitudes towards long acting parenteral hepatitis C therapy (Long-Acting Hepatitis C Therapy Questionnaire).

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).

Study design (Figure 1)

This is an open label multicentre study. The study consists of a screening phase, treatment phase and follow-up phase to evaluate treatment response and reinfection. Participants will be required to wait a minimum of four weeks form screening before commencing treatment to assess for spontaneous clearance. The maximum wait period allowed between screening and baseline is 12 weeks.

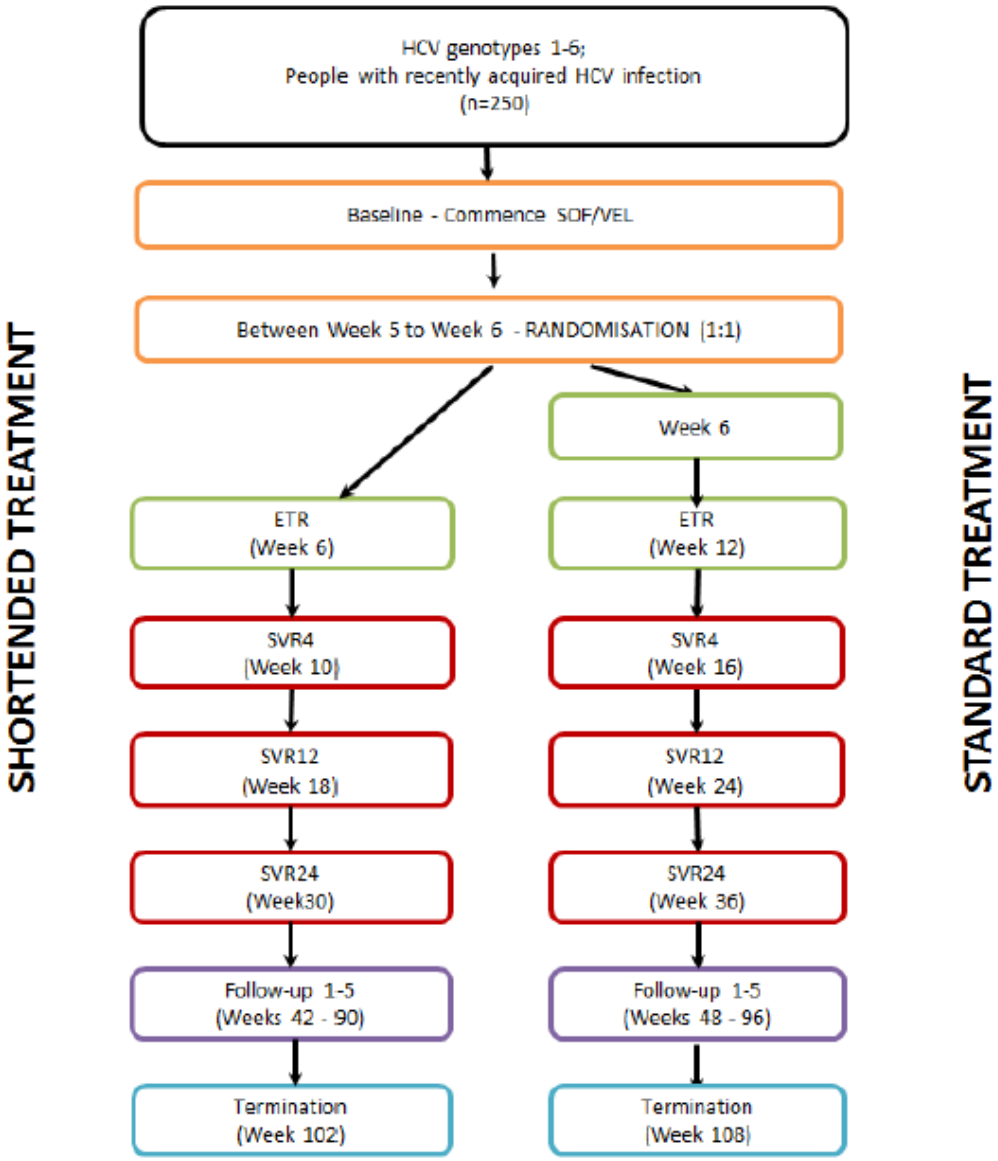

Figure 1: Study Schema

Sample size and power

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.

TYPE OF ANALYSIS

This document describes the primary statistical analysis for REACT study in accordance with protocol version 5.0.

Data Safety and Monitoring Board (DSMB) Analysis

This study has a DSMB to review the progress and safety of the study. The DSMB conducted an interim safety and adherence analysis when the first 50 participants had either reached post-treatment week 12 or dropped out of the study and then when a further 10 per arm reached 12 weeks post treatment. At the second review the DSMB recommended termination of the short arm of the study due to inferiority. At the stage of the DSMB recommendation, at total of 196 participants had been randomised, 192 had completed their randomised treatment, a further 4 were randomised to receive 6 weeks and extended to 12 weeks. Therefore, the primary analysis population will be based on 192 participants (99 in standard Arm, and 93 in shortened arm).

Primary analysis: Post-treatment week 12

The analysis for the primary endpoint, SVR12, will be conducted after all participants have completed the post-treatment week 12 visit or prematurely discontinue from study. All the safety and efficacy data through to the post-treatment week 12 visit will be cleaned, finalised, and included for the analysis.

GENERAL CONSIDERATIONS FOR DATA ANALYSES

Statistical Methods

Analysis results will be presented using descriptive statistics. For categorical variables, the number (n) and percentage of participants in each category will be presented. For continuous variables, the number of participants (n), mean and standard deviation (SD), median, interquartile range (IQR, Q1-Q3), range (minimum, maximum) will be reported; for inclusion in the manuscript, an appropriate determination will be made depending on the variable, size and distribution of the population studied.

Statistical tests will be 2-sided and performed at the 5% significance level unless specified.

For all efficacy endpoints, means and proportions with two-sided 95% confidence intervals (CI) will be determined. For the analysis of categorical outcomes, Chi-squared tests or exact equivalents (for small numbers) will be used. For comparison of continuous measures, t tests or non-parametric equivalents will be used as appropriate for the observed data distribution. Changes in injecting behaviour between screening, end of treatment and post-treatment week 12 will be compared using the McNemar test (exact binomial probability).

Analysis Sets

Analysis sets define the subjects to be included in an analysis. The number of participants eligible for each analysis set will be provided. Participants who were excluded from each analysis set will be summarised, with reasons for exclusion.

Full Analysis Set (ITT population)

The FAS includes all enrolled participants who were randomised. This will be the analysis set used for the primary efficacy and safety endpoints. Following the DSMB recommendation to cease the study, the primary analysis population will be based on 192 participants (99 in standard Arm, and 93 in shortened arm).

Modified Full Analysis Set

The modified Intention to Treat (mITT) population includes participants in the FAS excluding those with non-virological reasons for treatment failure (i.e., death, loss to follow up) and reinfection. Participants with confirmed reinfection after achieving an ETR, but prior to the primary efficacy endpoint (SVR12), will be excluded from the mITT.

Per-protocol Analysis Set

The PP population is defined as all participants who received >90% of scheduled treatment for >90% of the scheduled treatment period with follow-up virologic data to SVR12.

Safety Population

The Safety population includes all participants who randomised and will be analysed and presented according to the actual on-treatment monitoring arm received during the study.

The ITT population will be used for primary efficacy analyses, and the safety population will be used for all safety analyses.

Data Handling Conventions

Missing Data

For the analyses of categorical HCV RNA data, missing post-treatment HCV RNA data will have the missing data imputed. Missing on-treatment HCV RNA will have the missing data imputed up to the time of the last dose.

If a data point is missing and is preceded and followed in time by values that are "<LLOQ, TND," then the missing data point will be set to "<LLOQ, TND."

If a data point is missing, and preceded and followed by values that are "<LLOQ, target detected," or preceded by "<LLOQ, target detected" and followed by "<LLOQ, TND," or preceded by "<LLOQ, TND" and followed by "<LLOQ, target detected," then the missing value will be set to "<LLOQ, target detected."

If a data point is missing, and preceded and followed by values that are ">LLOQ, target detected," or preceded by ">LLOQ, detected" and followed by "<LLOQ, target detected" or "<LLOQ, TND", then the missing value will be set to ">LLOQ, target detected."

The following scenarios describe a framework for analysis of the primary endpoint based on various anticipated events for the ITT and mITT population:

i. In the event of the participant dying or becoming lost to follow-up prior to SVR 12, the participant will be considered to have failed treatment (loss to follow up = failure)

ii. If the SVR 12 time-point measure is missing, then the next available measure (i.e., SVR 24 or later) will be used. If no future time points are available, the participant will be considered a treatment failure.

Where appropriate, safety data for subjects who did not complete the study will be included in summary statistics.

For example:

- If a participant took at least 1 dose of study drug, the subject will be included in a summary of adverse events according to the treatment received; otherwise, if the subject is not dosed, then they will be excluded from the summary.
- If safety laboratory results for a participant are missing for any reason at a time point, the subject will be excluded from the calculation of the summary statistics for that time point.

Values for missing safety laboratory data will not be imputed; however, a missing baseline (day 0) result will be replaced with a screening result, if available.

Outliers

Outliers will be identified during data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

Data Handling Conventions and Transformations
HCV RNA values below the LLOQ for the assay will be set to the lower limit minus 1 for the calculation of summary statistics for the actual HCV RNA values and the change from baseline values by study visit.

For selected analyses, HCV RNA data (IU/mL) will be transformed to the logarithmic (base 10) scale (log_{10} IU/mL).

Visit Windows
Definition of Study Day
Study day will be calculated from the date of first dose of study drug administration and derived as follows:

- For post-dose study days: Assessment Date minus First Dose Date + 1
- For days prior to the first dose: Assessment Date minus First Dose Date

The last dose date for an individual study drug will be the end date entered in the Treatment Termination or Drug Administration eCRF.

The last dose date of treatment for a given participant will be defined as the maximum of the last dose dates of individual study drugs in a treatment group, if applicable.

If there are participants for whom the date of last study drug is unknown (lost to follow-up and not able to be contacted), the date of last dose will be estimated using the maximum of non-missing study drug start or stop dates, visit dates, and laboratory collection dates (post-treatment visits and unscheduled visits are not included).

Analysis Windows
Participant visits might not occur on protocol-specified days. Therefore, for the purposes of analysis, observations will be assigned to analysis windows (**Table 1** and **Table 2**).

In general, the baseline value will be the last non-missing value on or prior to the first dose date of study drug. HCV RNA and safety laboratory data collected up to the last dose date + ≤3 days are considered to be on-treatment data. HCV RNA and safety laboratory data collected after the last dose date + >3 days are considered post-treatment data. HCV RNA and safety laboratory data collected after the last dose date + >3 days will be assigned to the post-treatment follow-up (FU) visits. Visit windows will be calculated from the last dose date (ie, FU Day = collection date minus the last dose date) as shown.

Table 1. On-treatment visit analysis windows

Nominal visit			
	Nominal day	Lower Limit	Upper Limit
Baseline	1	NA	1
Week 2	14	8	21
Week 4	28	22	35
Week 6*	42	36	49
Week 8	56	50	63
Week 10	70	64	77
Week 12	84	78	≥85

***Shortened arm ETR**

Table 2. Post-treatment visit analysis windows

Nominal FU visit	HCV RNA			Safety Laboratory Data		
	Nominal day	Lower Limit	Upper Limit	Nominal day	Lower Limit	Upper Limit
PT week 4	28	21	69	28	4	30
PT week 12	84	70	146	NA	NA	NA
PT week 24	168	147	NA	NA	NA	NA

PARTICIPANT DISPOSITION

Recruitment

The following dates will be presented to define the period of recruitment and follow-up:

I. first and last participant screened
II. first and last participant baselined
III. first and last participant to complete PT week 12

Participant Enrolment and Disposition

A summary of participant enrolment will be provided- overall and by treatment group (if appropriate). The total number of participants who were screened, enrolled and treated will be depicted by a flowchart (**Figure 2**).

A summary of participant disposition will be provided overall (**Table 3**).

Reasons for participant exclusion, including screen failure and loss to follow up, will be summarised (**Table 4, Table 5**).

Protocol violations

Number, proportion, type and reason for any protocol violations will be described (**Table 6**).

Figure 2. Participant disposition

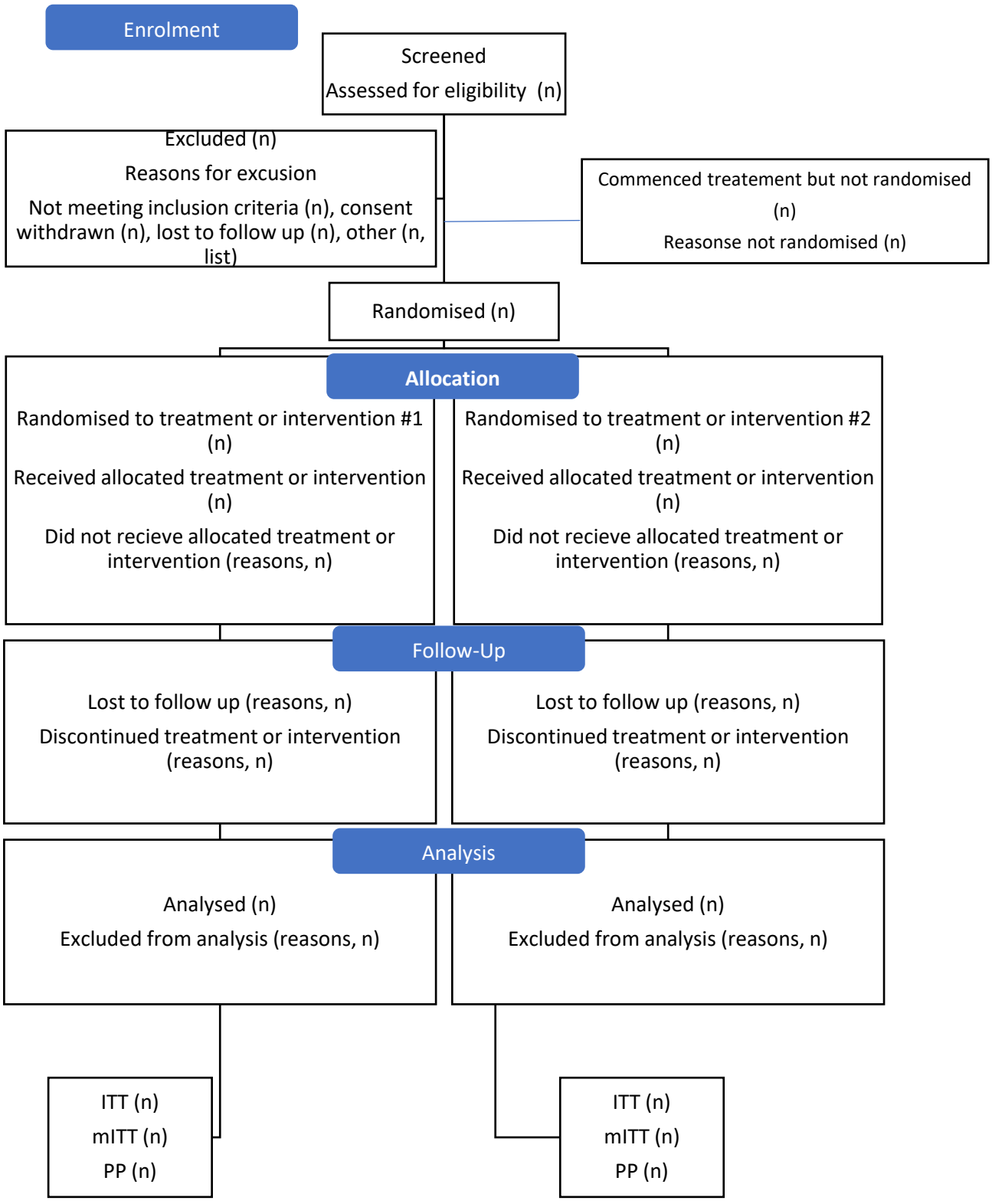

Table 3. Recruitment and follow-up

Participant disposition	Total N (%)	Standard arm N(%)	Shortened arm N(%)
Total participants screened, n			
Participants screened and excluded, n			
Participants allocated to treatment, N			
Commenced allocated treatment, n/N (%)			
Did not commence allocated treatment, n/N (%)			
Treated Participants			
Completed allocated treatment course, n (%)			
Discontinued treatment, n (%)			
Lost to study follow-up, n (%)			
Study follow up			
Completed study follow up, n (%)			
Did not complete study follow up, n (%)			
Population for analysis			
ITT, n			
mITT, n			
PP, n			

Table 4. Reasons for screen failure

Participant disposition	N (%)
Total participants screened, n	
Participants screened and excluded, n	
Screen fail participants who did not meet eligibility criteria	
List reasons (inclusion and exclusion criteria)	
Participants who met eligibility criteria but were not enrolled	
List reasons for not being enrolled	
Lost to follow up	
Withdrew consent	

Table 5. Reasons for loss to study follow-up

Study Number	Date of treatment commencement	Date last follow-up	Reason lost to follow-up
Standard Arm			
Simplified Arm			

Table 6. Protocol violations or deviations

Protocol violations or deviations	N (%)
Total number with protocol violations	
Total number with protocol deviations	
Violation of study inclusion or exclusion criteria	
Enrolment errors	

BASELINE DATA

Demographic Data and Baseline Characteristics (Table 7 - 11)

Demographic and baseline measurements will be summarized using standard descriptive methods. Baseline data will be summarised for the total FAS population and by HCV genotype and HIV serostatus as: number (n) and proportion for categorical parameters; or n, mean and standard deviation (SD), median, Q1, Q3, minimum and maximum for continuous parameters.

Age will be calculated in years at the date of initial study drug administration (baseline).

P values will not be reported for differences between the two groups at baseline, since appropriate randomisation methods will have accounted for this. Any differences identified would be due to chance such that a significant *p* value would in reality be representative of a type 1 error. Large differences at baseline (more than half a SD for continuous variables or 10% for categorical variables) will be investigated in a sensitivity analysis.

For pre-specified variables and variables only recorded at screening and not at baseline, screening values will be presented in the baseline table.

Table 7. Participant demographic and clinical enrolment characteristics

Enrolment characteristics	Total study population (n=XXX)	Standard Arm (n=XXX)	Shortened Arm (n=xxx)
Age, mean (SD) or median (IQR)			
Gender, n (%)			
Male			
Female			
Transgender			
Ethnicity, n (%)			
Caucasian/white			
Asian			
Black			
Other			
BMI, mean (SD) or median (IQR or range)			
HCV genotype/subtype, n (%)			
Genotype 1			
1a			
1b			
1, not specified			
Genotype 2			
2a			
2b			
Genotype 3			
3a			
Genotype 4			
Genotype 5			
Genotype 6			
Genotype mixed			
Specify			
Genotype indeterminate			
HCV RNA, IU/mL			
Quantitative, mean (SD) or median (IQR or range)			
Log10, mean (SD) or median (IQR or range)			
Classification of recent HCV Infection			
Primary			
Reinfection			
Duration of infection, mean (SD) or median (IQR or range)			
Acute			
Chronic			

Table 8. Other baseline demographic and socio-economic characteristics

Variable	Total	Standard arm	Shortened arm
Sexuality, n (%)			
Source of income, n (%)			
Highest level of education, n (%)			
Accommodation, n (%) Rented house/flat; privately owned house/flat; boarding house; hostel; psychiatric home; alcohol/drug treatment residence; shelter/refuge; prison/detention centre; caravan; no usual residence, squat; other			
Social functioning score, mean (SD) or median (IQR)			
Who do you live with? Alone; spouse partner; Alone with children; spouse/partner and children; other relatives; friends; friends/parents/relative and children; other			
Been in prison/juvenile justice, n(%) Ever; last 6 months			
Clinician determined mode of HCV exposure, n (%)			
Self-reported mode of HCV exposure, n (%) Injecting drug use/ Transfusion of blood products/ Occupational (needle stick or other exposure)/ Sexual exposure to a known HCV positive person of the same sex/ Sexual exposure to a known HCV positive person of the opposite sex/ Sexual exposure to persons of unknown HCV status of the same sex/ Sexual exposure to persons of unknown HCV status of the opposite sex/ Body piercing/ Tattoos/ Use of recreational drugs (snorting/inhaling)/ Other (please specify)			
PrEP use in past 6 months (among HIV negative), n(%) Never/ Yes every day/ Yes every week (4-6 days per week)/ Yes every week (1-3 days per week)/ Yes, occasionally (the day or two before or after sex)			
Screened for STDs in last 12 months, n (%)			
STD diagnosed in last 12 months prior to HCV diagnosis, n(%) Listing of STDs among those diagnosed			

Table 9. Participant viral enrolment characteristics

Baseline characteristics	**Total study population N=XXX**	**Standard Arm N=XXX**	**Shortened Arm N=XXX**
HCV			
ALT (U/L), median (IQR) Peak ALT prior to enrolment ALT at baseline			
Prior HCV treatment, n (%) Yes (Specify)			
Response to prior HCV treatment, n/total "Yes" (%) Non-response Breakthrough Relapse Other (specify)			
Fibroscan performed, n (%) Valid Fibroscan, n/N (%)			
Median liver stiffness measurement (Fibroscan®), kPa (IQR) (in those with **valid** Fibroscan result only)			
HIV			
HIV infection, n (%) CD4 count (10^6/L), median (IQR) HIV VL ≤50 at screening, n (%) On cART, n (%)			
HBV			
HBsAg positive, n (%) HBcAb positive, n (%) HsAb >10 IU/ml, n (%) HBV DNA detected, n (%) NA therapy for HBV, n (%)			

Abbreviations: Combination antiretroviral therapy (cART); nucleos(t)ide analogue (NA)

Table 10. History of substance use at enrolment

Substance use characteristics	Total N=	Standard Arm N=	Shortened Arm N=
Injecting drug use, n (%)			
Ever			
..Recent [a]			
Current [a]			
In those reporting injecting drug use:			
Age at first injecting, median (range)			
Last injected within 30 days, n (%)			
Last injected between 1-6 months ago, n (%)			
Last injected >6 months ago, n (%)			
If injected in the previous 1 month, frequency (n, %):			
>3x most days			
.2-3x most days			
.. Daily			
More than weekly, but less than daily			
Less than weekly			
Drug injected most in last month, n (%) [b]			
Heroine			
.. Cocaine			
.. Methamphetamines			
.. Other opiates			
.. Benzodiazepines			
Opioid substitution therapy, n (%)			
Never			
.. Ever			
.. Cot currently			
Current			
Alcohol use, n (%)[c]			
None			
Frequency n (%)			
Monthly or less;			
2 - 4 times/month			
2 -3 times/week			
4 or more times/week			
Standard drinks per day n (%)			
Mean (SD); Median (IQR)			
Frequency of Six or more standard drinks on one occasion n (%)			
Never, less than monthly, monthly, weekly, almost daily/ daily			
AUDIT C Score n (%)			
Number identified as hazardous drinkers n (%)			

[a] Recent injecting drug use refers to use within 6 month of screening, and Current injecting within the past month; [b] other drugs not listed that will also be summarised: Oxycodone, methadone, buprenorphine, fentanyl, steroids, LSD or other hallucinogens, Ecstasy; [c] One standard drink = 10 grams of alcohol

Table 11. Of syringe sharing among Injecting drug users

Syringe sharing use characteristics [a]	**Total N=**	**Standard Arm N=**	**Shortened Arm N=**
Use of NEW sterile needle and syringe in last month, n (%)			
All injections			
..Most of the time [a]			
Half of the time			
Some of the time			
Not in the last month			
How many times in last month used a needled/syringe after someone else, n (%)			
None			
One time			
Two times			
3 – 5 times			
More than 5 times			
Who did you share with?, n (%)			
No-one			
Regular sex partner			
Casual sex partner			
Close friends			
Acquaintance			
Other			
How many times in last month has someone used a needled/syringe after you, n (%)			
None			
One time			
Two times			
3 – 5 times			
More than 5 times			
Who were these people that shared after you?, n (%)			
No-one			
Regular sex partner			
Casual sex partner			
Close friends			
Acquaintance			
Other			

[a] Denominator – those reporting injecting drug use in last month

STUDY ENDPOINTS

Table 12. Study endpoints and outcomes

Primary endpoint	Non-inferiority of simplified on-treatment monitoring to standard on-treatment monitoring (ITT population)	Included in primary analysis
Secondary endpoints	Non-inferiority of simplified on-treatment monitoring to standard on-treatment monitoring (mITT population)	Included in primary analysis
	Non-inferiority of simplified on-treatment monitoring to standard on-treatment monitoring (PP population)	Included in primary analysis
	Treatment response: ETR, SVR4, SVR24; HCV RNA below the level of quantification through 2 years post treatment	Included in primary analysis
	Adverse events	Included in primary analysis
	On-treatment adherence	Included in primary analysis
	Early treatment discontinuation	Included in primary analysis
	Relapse and reinfection	Included in primary analysis
	Resistance associated substitutions (RAS) for people who have failed treatment	Included in primary analysis
	Laboratory abnormalities	Included in primary analysis
	Change in HIV RNA and CD4 (on treatment and end of treatment)	Included in primary analysis
		Included in primary analysis
Additional pre-specified outcomes	Factors associated with on treatment efficacy (only if SVR12 is low)	Included in primary analysis
	Factors associated with sub-optimal adherence	
	Factors associated with re-infection	Not included in primary analysis
	To evaluate the impact of treatment on illicit drug use, injecting behaviour and sexual risk-taking behaviour (behavioural survey) during treatment	Not included in primary analysis
	To evaluate patient interest and attitudes towards long acting parenteral hepatitis C therapy (Long-Acting Hepatitis C Therapy Questionnaire)	Not included in primary analysis

Primary efficacy endpoint
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)

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).

Secondary efficacy endpoints
- Virological endpoints
    - The proportion of treated participants with:
        - ETR (defined as undetectable plasma HCV RNA at the end of treatment)
        - SVR4 (defined as undetectable plasma HCV RNA at post-treatment week 4)

For virological endpoints, the point estimates and 95% exact confidence intervals will be reported by study arm, by HCV genotype and by HIV serostatus.

Virological endpoints (Table 13 and 14)
The presence of HCV RNA will be assessed at all scheduled clinic study visits using Aptima HCV Quant Dx assay, version 2.15.5 (lower limit of quantitation [LLoQ] 10IU/mL; Hologic, Inc., Marlborough, MA, USA), with centralised testing performed at St Vincent's Centre for Applied Medical Research (Sydney, NSW, Australia).

Proportions and 95% confidence intervals will be reported for both the primary and secondary virological endpoints. Virological endpoints will be assessed in the ITT, mITT and PP populations, with results stratified by HCV genotype/subtype and HIV serostatus.

Factors associated with treatment outcome in the ITT population will be evaluated by univariate analysis. Variables assessed will include but are not limited to: demographic factors (age, gender); virological factors (baseline HCV RNA, genotype 1 subtype, duration of HCV infection); risk behaviors (injecting drug use, sexual behavior, mode of HCV acquisition); HIV co-infection; treatment factors (adherence).

Primary safety endpoints
The primary safety endpoints are:
- Proportion of participants with common adverse events (reported by greater than 5% of the study population);
- Proportion of participants with at least one severe or potentially life threatening (grade 3 or 4) adverse event;

Adherence
80% adherence: Defined as the receipt of >80% of scheduled doses.
90% adherence: Defined as the receipt of >90% of scheduled doses.
100% adherence: Defined as the receipt of 100% of scheduled doses.

On-treatment adherence will be 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.

Table 13. Primary and secondary efficacy endpoints – (ITT)

Efficacy	Arm A Standard treatment (N=XX)	Arm B Shortened treatment (N=XX)	Difference between arms (95% CI)	P value
ETR, n (%)				
SVR 4, n (%)				
SVR 12, n (%) Non-response Relapse Reinfection Lost to follow up				
SVR 24, n (%)				
Virologic failure, n (%) On-treatment failure (non-response, breakthrough) Relapse*			NA	

***relapse definition:**

Analysis tables will also be presented for the mITT, and PP populations

Table 14. SVR12 in participant subgroups, ITT population

Subgroup	Standard tx arm n/N (%; 95% CI)	Shortened tx arm n/N (%; 95% CI)
HCV mono-infection		
HIV/HCV co-infection		
Genotype 1		
Genotype 1a		
Genotype 1b		
Genotype 2		
Genotype 3		
Genotype 4		
Genotype 5		
Genotype 6		

Other secondary outpoints

Table 15: Primary reason for premature discontinuation of study drug

Reason for premature discontinuation, n (%)	**Standard tx arm (n=XXX)**	**Shortened tx arm (n=XXX)**
Adverse event		
Non-compliance		
Withdrawal of consent		
Loss to follow up		
Other *Specify - list*		

Table 16: Reinfection by SVR12

	N	%	95% CI
Standard Arm			
Shortened Arm			

Table 17: Relapse by SVR12

	N	%	95% CI
Standard Arm			
Shortened Arm			

Table 18. Prevalence of polymorphisms in NS5B and NS5A at baseline

Polymorphism, n (%)	**Total study population N=XXX**	**Standard duration arm N=XXX**	**Shortened duration arm N=XXX**
Any NS5B	**N**	**N**	**N**
[Specify]			
Any NS5A	**N**	**N**	**N**
M28G/S/T L31F/I/M/P/V P32A/L/Q/R A/C92K/T Y93D/H/N/R/S/W			

Baseline polymorphisms detected by Sanger sequencing at the following amino acid positions:
NS5A: 28, 31, 32, 92, 93

Table 19. NS5B and NS5A polymorphisms at baseline and virologic failure

Subject ID	Genotype and subtype	Virologic failure	NS5B Variants		NS5A variants	
			Baseline	Failure	Baseline	Failure
Standard treatment duration (12 weeks), n=XXX						
Shortened treatment duration (6 weeks), n=XXX						

Table 19. Characteristics of participants with virological failure

Subject ID	Genotype and subtype	Virologic failure	Genetic distance % [1]		Baseline HCV RNA (log_{10})	Adherent[2]
			Core-E2[1]	NS5A		
Standard treatment duration (12 weeks), n=XXX						
Shortened treatment duration (6 weeks), n=XXX						

1. Reported genetic distance % for Core-E2 and NS5A was the comparison between sequences at baseline and post-treatment week 12. Cut-off for homologous virus was <4% for Core-E2 and X% for NS5A.

2. Adherence was defined as receipt of ≥95% of the prescribed treatment course

Table 21. On treatment adherence

	N	%	95% CI
80% adherence			
Standard Arm			
Shortened Arm			
90% adherence			
Standard Arm			
Shortened Arm			
100% adherence			
Standard Arm			
Shortened Arm			

SAFETY ANALYSES
All participants who receive at least one dose of study drug will be included in the safety analyses. Safety analyses will be performed overall and by treatment arm. Safety will be evaluated by assessment of clinical laboratory tests at various time points during the study, and by the documentation of AEs.

All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug will be summarised.

Extent of Exposure
A participant's extent of exposure to study drug will be generated from the study drug administration page of the eCRF.

Adverse Events
Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, insert version). System organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT) will be provided.

Events will be summarised on the basis of the date of onset for the event.

A treatment-emergent AE (TEAE) will be defined as:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug

Adverse Event Severity
Adverse events are graded by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4) according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings, and the most severe will be considered (for sorting purpose only) in data presented. For example, if an adverse event of the same type (PT) is listed more than once for an individual, the highest grade will be used to summarise severity.

Relationship of Adverse Events to Study Drug
Related AEs are those for which the investigator selected "Related" ("Possibly related" or "Probably related") on the AE CRF to the question of "Related to Study Treatment." Events for which the investigator did not record the relationship to study drug will be considered to be related to study drug for summary purposes.

Summaries of Adverse Events and Deaths
The number and percentage of participants overall and in each arm with treatment-emergent adverse events will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT). The tabulation of the number of participants with treatment-emergent adverse events by severity grade and relationship to study drug also will be provided.

Participants reporting more than one adverse event for a given MedDRA PT will be counted only once for that term using the most severe grade for the severity grade table and the most related for

the relationship to study drug tables. Participants reporting more than one type of event within a SOC will be counted only once for that SOC, but both PTs will be listed.

Summaries of treatment-emergent AEs (by SOC and PT) will be provided for the following:

- All TEAEs
- TEAEs of Grade 3 or above
- All treatment-related TEAEs
- Treatment-related TEAEs of Grade 3 or above
- All SAEs (including death)
- All treatment-related SAEs
- All TEAEs leading to premature discontinuation of the study drug
- TEAEs that occurred in at least 5% of subjects within any treatment group

Adverse event summaries will provide the number and percentage of subjects with treatment-emergent AEs by SOC and PT, divided by treatment group.

Adverse events will be summarised and listed first in alphabetic order of SOC and then by PT in order of descending incidence of the pooled treatment groups within each SOC.

In summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in a participant during the study.

Serious adverse events (SAE)
The proportion of participants with at least one SAE will be reported overall. Serious adverse events will be summarized and relationship between the SAE and study drug will be detailed

Laboratory Evaluation
Selected laboratory data will be summarised (n, mean, SD, median, IQR, range) by study visit along with the corresponding change from Baseline/Day 1 to Post Treatment Week 12.

Depending on sample distribution, parametric or non-parametric tests can be used to compare the change in biochemical and haematological indicators over time.

The NIH DAIDS AE Grading Table Version 2.0- November 2014 will be used to grade severity.

Table 22. Safety parameters – adverse events and treatment discontinuation

Adverse events	**Safety analysis set (N=XX)**
Participants reporting any AE up to 30 days after last dose, n (%) Grades 1-2, n (%) Grade 3, n (%) Grade 4, n (%)	
Participants reporting treatment-related AE up to 30 days after last dose, n (%) Grades 1-2, n (%) Grade 3, n (%) Grade 4, n (%)	
Serious adverse event, n (%)	
Treatment-related serious adverse event, n (%)	
Treatment discontinuation due to adverse event, n (%)	
Death, n (%)	
Adverse events *Common (>10% of study population), n (%)* Specify (list)	

Table 23. Listing of serious adverse events

Study Arm	**Date Onset**	**Date resolved**	**Diagnosis or event description**	**SAE criteria‡**	**Outcome§**	**Relationship to study drug**
Standard						
Shortened						

‡ Death, hospitalised, life threatening, medically important, congenital anomaly, disability
§ Recovered, Improved, Unchanged, Worsened, Unknown, Died

Table 24. Serious adverse events summary

SAE – event summary	**All N=XXX**	**Treatment arm 1 N=XXX**	**Treatment arm 2 N=XXX**
N of participants experiencing any treatment-emergent SAE by MedDRA SOC and Preferred Term, n (%) SOC (alphabetical order) List PT			

Laboratory Evaluation

Selected laboratory data will be summarised (n, mean, SD, median, IQR, range) by study visit along with the corresponding change from Baseline/Day 1.

Table 25. Summary table for key laboratory evaluations

Lab parameter	N	Mean	SD	Min	Q1	Median	Q3	Max
ALT								
AST								
Glucose								
ALP								
Albumin								
Creatinine								
Haemoglobin								
WBC								
Neutrophils								
Platelets								
Bilirubin								

*table will be further stratified by Arm and study weeks (Screening, baseline, Week 4, ETR, SVR4)

Table 26. HIV patients only – changes in HIV viral load and CD4 cell count

Parameter	Standard Arm	Shortened arm
HIV viral load (<20 copies)	**N (%)**	**N (%)**
Screening		
Baseline		
Week 4		
SVR12		
Change in CD4 cell count	**Mean (SD)**	**Mean (SD)**
Screening		
Baseline		
SVR12		

Table 27. Listing of HIV patients with VL > 200 copies at any timepoint, by treatment arm

Study Arm	Study ID	Week first VL >200 copies/mL
Standard		
Shortened		

Table 28. Grading of severity of laboratory measures

Laboratory evaluation	**Standard Arm (N=XX)**	**Shortened Arm (N=XX)**
Haematological parameters		
Baseline Hb, g/L (mean, SD)		
Change in Hb at post-treatment week 12, g/L (mean, SD)		
Haemoglobin [#], n (%) Grade 2 Grade 3 Grade 4		
Biochemical parameters		
Baseline ALT, U/L (mean, SD)		
ALT, n (%) Grade 2 (3-5x ULN) Grade ≥3 (>5x ULN)		
Change in ALT at post-treatment week 12, g/L (mean, SD)		
Baseline AST, U/L (mean, SD)		
AST, n (%) Grade 2 (3-5x ULN) Grade ≥3 (>5x ULN)		
Change in AST at post-treatment week 12, g/L (mean, SD)		
Baseline total bilirubin, mg/dl or mmol/L (mean, SD)		
Total bilirubin *, n (%) >2.5-3.0 mg/dl (43 – 51 mmol/L) >3.0 mg/dl (>51 mmol/L)		
Change in bilirubin at post-treatment week 12, g/L (mean, SD)		

[#] At any time during treatment and up to 30 days post; each participant should only be included once - record most severe grade of anaemia for each participant

*At any time during treatment and up to 30 days post; add footnote, if bilirubin elevated at screening/baseline