Simplified Monitoring - A Randomised Trial in hepatitis C

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

EUDRACT: 2017-00694-37 / ClinicalTrials.gov Identifier: NCT03117569

Statistical Analysis Plan

Study Title:	Simplified Monitoring – A Randomised Trial in hepatitis C
Name of Study Drug:	Glecaprevir/Pibrentasvir (300mg/120mg)
Protocol Number:	VHCRP1701
Protocol Version:	2.0
Protocol Date:	14 June 2017
Co-ordinating Principal Investigators:	Professor Gregory Dore
Name/s of Sponsor:	UNSW Sydney
Analysis Type:	Primary analysis
Analysis Plan Version:	1.0
Analysis Plan Date:	9 July 2018
Analysis Plan Author:	Dr Marianne Martinello

Contents

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
APRI	AST:platelet ratio index
APTT	activated partial thromboplastin time
ARV	antiretroviral
AST	aspartate aminotransferase
BLoQ	below the lower limit of quantitation
cART	combination antiretroviral therapy
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
ITT	intention-to-treat
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
mITT	modified intention-to-treat
mITT-VF	modified intention-to-treat, virological failure
PP	per-protocol
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

INTRODUCTION

The capacity to scale-up interferon-free DAA therapy would be enhanced by simplified treatment monitoring strategies. The "next generation" DAA regimen of glecaprevir/pibrentasvir, an NS3/4a protease inhibitor and an NS5A inhibitor, provide key features for HCV treatment simplification, including on-treatment monitoring: 1) pan-genotypic activity with very high efficacy (SVR>95%); 2) no relationship between time to undetectable HCV RNA and SVR; 3) minimal drug-related toxicity; 4) ease of dosing (three pills once daily); and 5) short duration (8 weeks for HCV treatment naïve individuals without cirrhosis; 12 weeks for HCV treatment naïve individuals with cirrhosis).

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

In people with chronic HCV (genotypes 1-6) who are treatment naïve and do not have cirrhosis, we hypothesise that the proportion achieving SVR following glecaprevir/pibrentasvir for 8 weeks with a simplified monitoring schedule will be non-inferior to glecaprevir/pibrentasvir for 8 weeks with a standard monitoring schedule.

This document describes the statistical analysis to be performed for the primary analysis of the SMART-C study, protocol version 2.0.

The analysis for the primary endpoint will be conducted after all participants complete 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. Prior to analyses, the study database will be locked in accordance with VHCRP Standard Operating Procedures and will have completed required quality assurance.

The primary analysis will focus on the non-inferiority of eight weeks of glecaprevir/pibrentasvir for treatment naïve patients without cirrhosis administered with simplified on-treatment monitoring strategy compared with a standard on-treatment monitoring strategy.

STUDY DEFINITIONS

Chronic HCV infection is defined by detection of anti-HCV antibody and/or HCV RNA for greater than six months prior to screening.

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 HCV RNA below the LLoQ (TND or TDnq) at the end of treatment (date of treatment cessation).

HCV treatment outcome will be classified as:

- *Sustained virological response at 12 weeks post-treatment (SVR12):* Defined as HCV RNA below the LLoQ (TND or TDnq) at 12 weeks post cessation of treatment.
- *Virologic failure:* Defined as HCV RNA above the LLoQ at 12 weeks post cessation of treatment (excluding reinfection).
    - In the ***standard monitoring arm***, HCV virologic failure will be further defined as one of the following:
        - *Non-response* (failure of virological suppression on-treatment with quantifiable HCV RNA at all time points measured between baseline and end of treatment).
        - *Breakthrough* (an increase from non-quantifiable to quantifiable HCV RNA or to at least 1 $\log_{10}$ above nadir while on treatment).
        - *Post-treatment relapse* (the presence of quantifiable HCV RNA after end of treatment with detection of infection with an HCV strain consistent with the primary infecting strain, confirmed as homologous virus on sequencing).
- *Non-virologic failure:* Defined as death, premature treatment discontinuation, loss to follow up or missing plasma HCV RNA at post treatment week 12.
- *Reinfection:* Defined as HCV RNA above the LLoQ after end of treatment with detection of infection with an HCV strain that was distinct from the primary infecting strain, confirmed as heterologous virus on sequencing.

STUDY OBJECTIVES AND DESIGN

Study objectives

The *primary objective* of this study is:

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

The *secondary objectives* of this study are:

- To compare the proportion of patients achieving SVR12 between those who received a standard versus simplified schedule of safety and virological monitoring, in the modified intention-to-treat population;
- To compare the proportion of patients achieving SVR12 between those who received a standard versus simplified schedule of safety and virological monitoring, in the per-protocol population;
- To evaluate the proportion adherent to treatment and study visits (on-treatment adherence and early treatment discontinuation);
- To evaluate patient reported outcomes following treatment;
- To evaluate safety and tolerability by monitoring adverse events during treatment;
- To evaluate patient treatment satisfaction;
- To evaluate the prevalence and impact of baseline resistance associated substitutions (RAS) on efficacy (SVR12);
- To evaluate cost-effectiveness of simplified monitoring;
- To evaluate immune-virological factors associated with SVR12.

The *exploratory objective* of this study is:

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

Last dose of study drug refers to the last dose of glecaprevir/pibrentasvir and will be used in the definition of treatment-emergent adverse events and laboratory abnormalities, as well as the primary efficacy endpoint (SVR12).

Study design

SMART-C is a Phase IIIb multicentre international randomised controlled trial. All participants will attend the study site for screening and baseline visits. Randomisation to study arm will occur at the baseline visit (**Figure 1**).

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

- Participants in the ***standard monitoring arm*** will have on-treatment study visits conducted at the site at weeks 4 and 8 (End of Treatment [EoT]).
- Participants in the ***simplified monitoring arm*** will have no on-treatment study visits conducted at the site.

Phone contact between the participant and site study nurse will occur in both arms 1-2 days prior to week 4 and week 8 (EoT) to provide standardized reporting of adverse events, concomitant medication and adherence.

One post treatment clinic visit will be conducted at post-treatment week 12 for all participants.

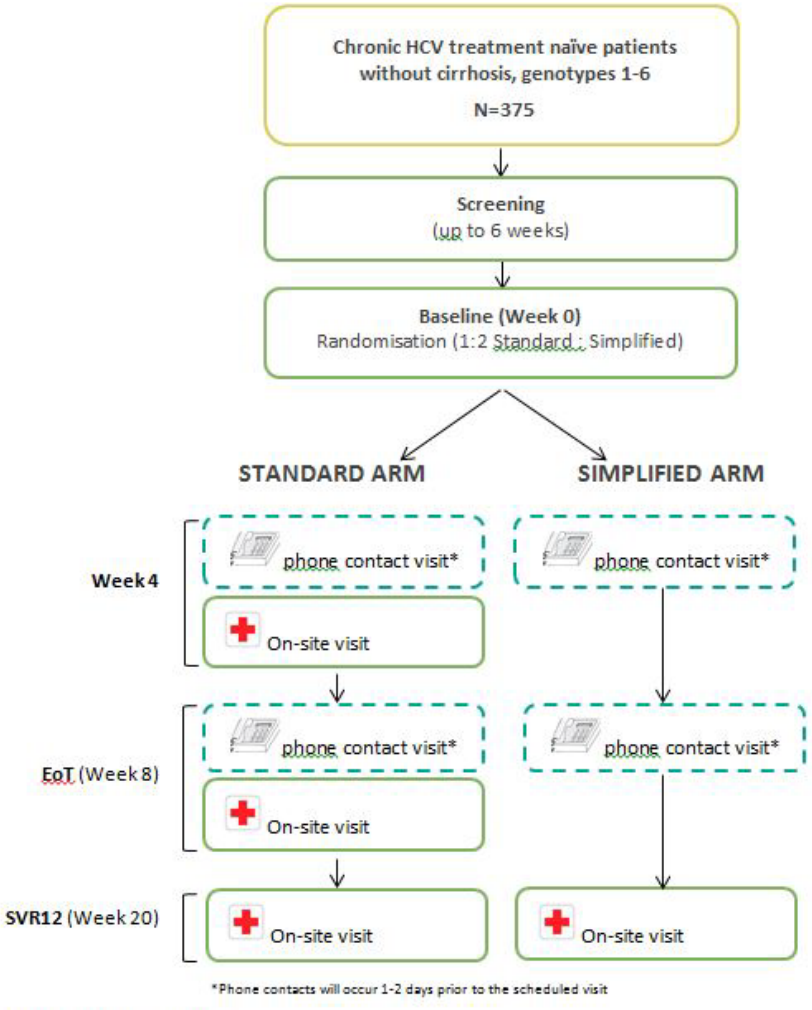

Figure 1 Study Schema

Sample size and power

The study was designed to enrol a total of 375 participants with genotype 1-6 HCV infection who had not received previous HCV treatment and did not have cirrhosis, randomised 2:1 - 250 participants in the simplified monitoring arm and 125 participants in the standard monitoring arm.

With these participant numbers and under the assumption that the proportion achieving SVR12 would be 96% in both arms, the study would have approximately 80% power to show non-inferiority of the simplified monitoring strategy to the standard monitoring strategy, with a lower confidence bound for SVR12 in the standard monitoring arm greater than 90% or with a lower confidence bound for the difference (simplified arm minus standard arm) in SVR12 greater than –6%. The 90% threshold for non-inferiority of the eight weeks glecaprevir/pibrenatasvir with standard monitoring was based on the clinical trial data available at the time of study design (SVR12 96%), minus a 6% non-inferiority margin.[1,2] The non-inferiority margin of 6 percentage points was selected in accordance with the principles outlined in guidance on conducting non-inferiority trials[3,4]; the choice of margin ensured minimal to no loss of efficacy.

TYPE OF ANALYSIS

This document describes the primary statistical analysis for SMART-C study in accordance with protocol version 2.0.

Data Safety and Monitoring Board (DSMB) Analysis

This study has a DSMB to review the progress and safety of the study. The DSMB will conduct an interim safety and adherence analysis when the first 75 participants have either reached post-treatment week 12 or dropped out of the study. Additional meetings may be considered by the DSMB at a frequency commensurate with the risk as determined by the DSMB.

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 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.

For the primary analysis of non-inferiority, the percentage of participants achieving SVR12 in each arm and the difference in percentages of participants achieving SVR12 between study arms will be calculated with confidence intervals using the normal approximation to the binomial distribution.

Non-inferiority of the 8-week regimen of glecaprevir/pibrentasvir with a simplified monitoring strategy to the 8-week regimen of glecaprevir/pibrentasvir with a standard monitoring strategy with regard to the proportion achieving SVR12 will be shown if the lower bound of the confidence interval for the differences is above the non-inferiority margin of −6 percentage points.

Analysis Sets

Intention-To-Treat (ITT) Population

The ITT population includes all participants who received at least one dose of study drug and will be analysed and presented by the on-treatment monitoring arm assigned at randomisation.

Modified Intention-To-Treat (mITT) Population

The mITT population excludes participants who have completed treatment (>95% adherence) (according to phone contact at week 8), but have not attended follow up at post-treatment week 12.

Modified Intention-To-Treat Virologic Failure (mITT-VF) Population
The mITT population includes participants in the ITT population with SVR12 or virologic failure, but excludes participants with non-virologic failure or reinfection.

Per-Protocol Population
The per-protocol population includes all participants who completed the 8-week regimen of glecaprevir/pibrentasvir (with >95% adherence, according to phone contact at week 8) and attended follow up at post-treatment week 12.

Safety Population
The Safety population includes all participants who received at least one dose of study drug 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
In general, missing data will not be imputed unless methods for handling missing data are specified. For the primary efficacy endpoint, participants with missing data will be analysed as missing equals failure.

Where appropriate, safety data for participants 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 participant will be included in a summary of adverse events according to the treatment received; otherwise, if the participant 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 participant 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.

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 of the study drug will be the end date entered in the Treatment Termination or Drug Administration eCRF.

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. 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 on-treatment data. HCV RNA and safety laboratory data collected after the last dose date + >3 days are considered post-treatment data.

The following days are based on treatment start date and stop date for the on and post treatment period, respectively.

On-treatment

Nominal visit	Standard monitoring arm			Simplified monitoring arm		
	Nominal day	Lower Limit	Upper Limit	Nominal day	Lower Limit	Upper Limit
Baseline	1	NA	1	1	NA	1
Week 4	28	21	42	NA	NA	NA
Week 8	56	43	59	NA	NA	NA

*The protocol specifies that the visit window for Week 4 and Week 8 is plus or minus 3 days.

Post-treatment

Nominal visit	Standard monitoring arm			Simplified monitoring arm		
	Nominal day	Lower Limit	Upper Limit	Nominal day	Lower Limit	Upper Limit
PT week 12	84	70	NA	84	70	NA

*The protocol specifies that the visit window for Post Treatment Week 12 is plus or minus 14 days. As the post treatment week 12 visit is the final scheduled study visit, the upper limit for the post-treatment week 12 visit will not be specified, and instead will be set at study close.

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 post treatment week 12

Participant Enrolment and Disposition

A summary of participant disposition will be provided overall and by study arm (Table 1). The total number of participants who were screened, enrolled (randomised) and treated will be depicted by a flowchart (Figure 2). Reasons for participant exclusion, including screen failure and loss to follow up, will be summarised (Table 2, Table 3, Table 4).

Protocol violations/exemptions

Number, proportion, type and reason for any protocol violations will be described (Table 5). For this purpose, a protocol violation/exemption will be defined as any person who was enrolled in the study despite failing an inclusion criterion and/or meeting an exclusion criterion.

Table 1. Recruitment and follow-up

Participant disposition	Total N (%)	Standard N (%)	Simplified N (%)
Total participants screened, n		NA	NA
Participants screened and excluded, n		NA	NA
Participants allocated to treatment (randomised), 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			
Intention-to-treat, n			
Modified intention-to-treat, n			
Modified intention-to-treat virological-failure, n			
Per protocol, n			

Table 2. Reasons for screen failure

Participant disposition	Total 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	
Other	

Table 3. Proportion lost to follow-up

Study arm	Number randomised	Proportion lost to follow-up (n/N, %)
Standard Monitoring		
Simplified Monitoring		

Table 4. Reasons for loss to study follow-up

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

Table 5. Protocol violations or deviations

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

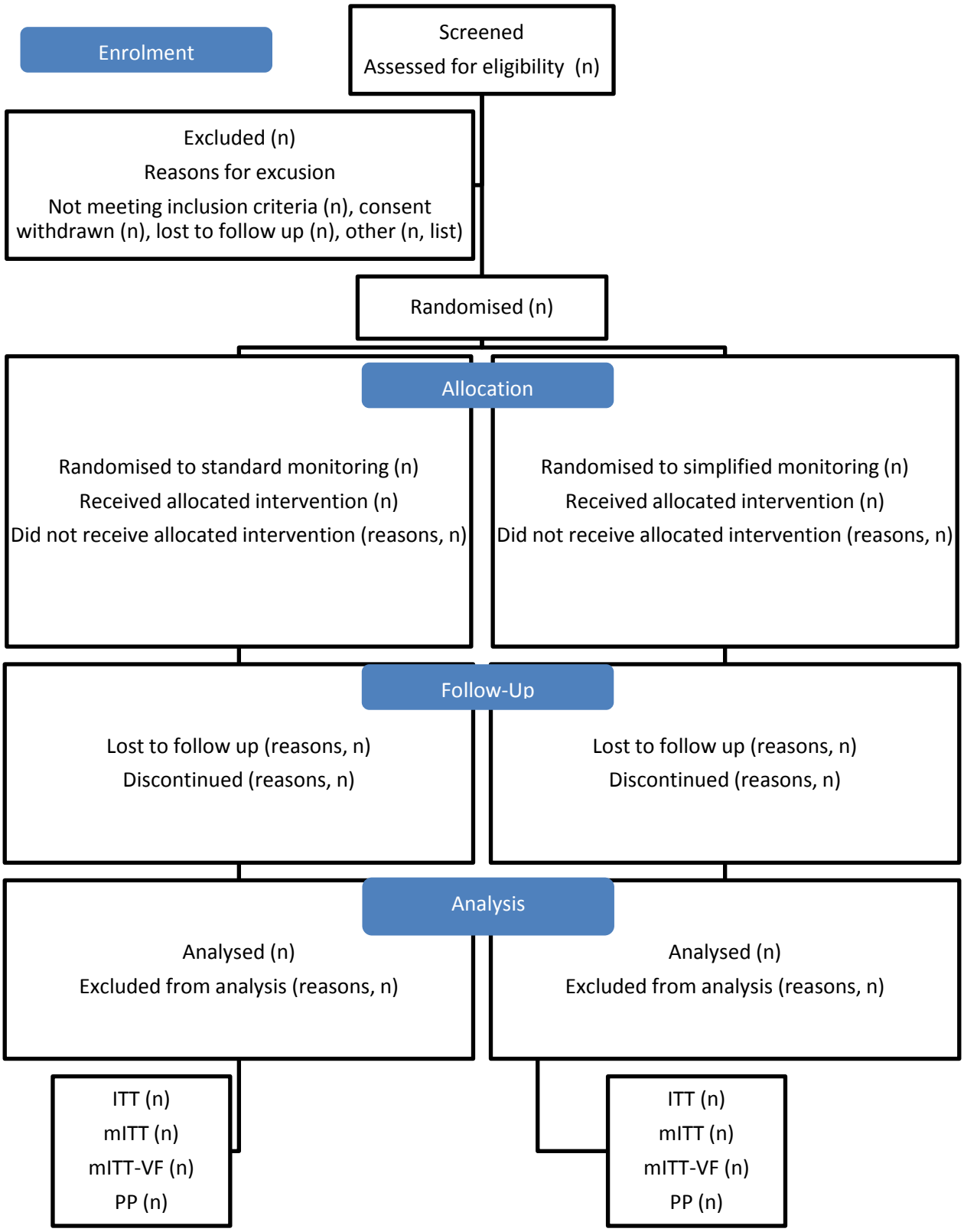

Figure 2. Participant disposition

BASELINE DATA
Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods (Table 6, Table 7).

Baseline data will be summarised for the ITT population and by study arm 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.

Prevalence of baseline polymorphisms in NS3 and NS5A will be summarised (Table 8).

Table 6. Baseline characteristics (ITT population)

Variable	Total study population (N=XXX)	Standard arm (N=XXX)	Simplified arm (N=XXX)
Age, median (range)			
Gender, n (%)			
Male			
Female			
Transgender			
Ethnicity, n (%)			
White			
Asian			
Black			
Other			
BMI, median (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, median (range)			
Log_{10}, median (range)			
HIV infection, n (%)			
Opioid substitution therapy, n (%)			

Table 7. Baseline viral characteristics

Baseline characteristics	Total study population (N=XXX)	Standard arm N=XXX	Simplified arm N=XXX
HCV			
Fibrosis stage determination, n (%) Transient elastography (Fibroscan) APRI			
Median liver stiffness measurement (Fibroscan®), kPa (range)			
Median APRI (range) APRI (by category), n (%) <0.5 (significant fibrosis unlikely) 0.5-1.5 (significant fibrosis likely)			
Fibrosis stage, n (%) No or mild fibrosis (F0/F1; LSM <7.1 kPa or APRI <0.5) Moderate fibrosis (F2; LSM 7.1-9.4 kPa or APRI 0.5 – 1.5) Severe fibrosis (F3; LSM 9.5-12.4 kPa)			
HIV			
HIV infection, n (%) CD4 count (10^6/L), median (IQR) HIV VL ≤50 at screening, n (%) On cART, n (%) *Specify regimen - list*			

Abbreviations: Combination antiretroviral therapy (cART)

Evaluation of fibrosis stage

If more than one measure was used, the hierarchy is as follows:

1. Transient elastrography (FibroScan) [5]
2. APRI

Table 8. Prevalence of polymorphisms in NS3 and NS5A at baseline

Polymorphism, n (%)	Total study population N=XXX	Standard arm N=XXX	Simplified arm N=XXX
Any NS3	**N**	**N**	**N**
Q80K/R R155T A156G/T/V A166T D/Q168A/K/L/R			
Any NS5A	**N**	**N**	**N**
K/Q/S24R/F M/L/F28A/G/K/T/V Q/R/K/A30D/E/R L/M/V31M P/H58D/T Y/T93H/N			

Baseline polymorphisms detected by Sanger sequencing at the following amino acid positions:
NS3: 36, 56, 155, 156, 166, 168
NS5A: 24, 28, 30, 31, 58, 93

STUDY ENDPOINTS

Table 9. 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 (per-protocol population)	Included in primary analysis
	Virologic failure	Included in primary analysis
	On-treatment adherence	Included in primary analysis
	Early treatment discontinuation	Included in primary analysis
	SVR12, by genotype	Included in primary analysis
	SVR12, by HIV serostatus	Included in primary analysis
	Adverse events	Included in primary analysis
	Laboratory abnormalities	Included in primary analysis
	Unscheduled clinic visits	Included in primary analysis
	Change from baseline in patient reported outcome summary measures	Included in primary analysis
	Presence of baseline polymorphisms	Included in primary analysis
	Presence of treatment-emergent substitutions in patients with virologic failure	Included in primary analysis
Additional pre-specified outcomes	Cost-effectiveness	Not included in primary analysis
	Health practitioner acceptability	Included in primary analysis

Primary efficacy endpoint

The primary efficacy endpoint is sustained virologic response at week 12 post treatment (SVR12), defined as plasma HCV RNA below the lower limit of quantitation (<10 IU/mL; target not detected [TND] or target detected, not quantifiable [TDnq]) at 12 weeks after the last dose of study drug in the ITT population.

The Aptima HCV Quant Dx assay, version 2.15.5 will be used to measure HCV RNA (Hologic, Inc., Marlborough, MA, USA). The LLOQ for this assay is 10 IU/mL.

The primary efficacy endpoint of SVR12 will be assessed within each arm, and the primary comparison of SVR12 will be for non-inferiority of the simplified monitoring arm compared to the standard monitoring arm (simplified arm minus standard arm).

Secondary efficacy endpoints
Secondary efficacy endpoints include:

- Proportion of participants achieving SVR12 in each arm (in the mITT, mITT-VF and per-protocol populations);
- Proportion of participants with virological failure;
- Proportion of participants who are adherent to treatment and study visits (on-treatment adherence and early treatment discontinuation);

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

Primary safety endpoint
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;
- Proportion of participants with unscheduled clinic visits.

Adherence
On-treatment adherence is recorded through self-reported adherence questionnaire at week 4 and week 8 (EoT) via phone contact visits, and by pill count at post-treatment week 12.
Study drug exposure and compliance will be summarised for all treated participants.

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 glecaprevir/pibrentasvir will be individually calculated at the 90/90, 95/95 and 100/100 adherence levels, defined as receipt of ≥90, ≥95 or 100% of scheduled doses for ≥90, ≥95 or 100% of the scheduled treatment period, respectively.

A participant will be considered compliant if the individual receives ≥95% of scheduled doses for ≥95% of the scheduled treatment period. The percentage of compliant participants will be summarised for each arm and overall.

Exploratory Analysis
Changes in quality of life data (EQ-5D-5L) and participant satisfaction will be compared at screening and post-treatment week 12 using the McNemar test (exact binomial probability).

Practitioner acceptability data will be compared at the time points of before FPFV and after LPLV at each site.

Table 10. HCV RNA response during and post treatment, ITT population

Response	Standard monitoring (N=XXX)	Simplified monitoring (N=XXX)	Difference between arms (95% CI)	*P*
HCV RNA <LLOQ, n (%) On treatment week 8 (end of treatment) Post treatment week 12		NA	NA	

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

Table 11. Treatment outcome, ITT population

Outcome	Standard monitoring (N=XXX)	Simplified monitoring (N=XXX)	Difference between arms (95% CI)	*P*
SVR12, n (%)				
Virologic failure, n (%) On-treatment failure (non-response, breakthrough) Post-treatment relapse		 NA NA	 NA NA	
Failure for other reasons, n (%) Discontinuation Loss to follow up or missing SVR12 data				

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

Table 12. SVR12 in participant subgroups, ITT population

Subgroup	Standard monitoring arm n/N (%; 95% CI)	Simplified monitoring arm n/N (%; 95% CI)
Male		
Female		
<65 years old		
≥65 years old		
BMI <30		
BMI ≥30		
HCV mono-infection		
HIV/HCV co-infection		
Genotype 1		
Genotype 1a		
Genotype 1b		
Genotype 2		
Genotype 3		
Genotype 4		
Genotype 5		
Genotype 6		
F0/F1 fibrosis		
F2 fibrosis		
F3 fibrosis		
Baseline HCV RNA ≥1,000,000		
Baseline HCV RNA ≥6,000,000		
Baseline HCV RNA ≥10,000,000		
On OST		

Table 13. Primary reason for premature discontinuation of study drug

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

Table 14. NS3 and NS4A polymorphisms at baseline and virologic failure

Subject ID	Genotype/subtype	Virologic failure	NS3 Variants		NS5A variants	
			Baseline	Failure	Baseline	Failure
Standard monitoring arm						
Simplified monitoring 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
- TAAEs 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 (Table 15, Table 16).

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 (Table 17, Table 18, Table 19).
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 15. Safety parameters – adverse events and treatment discontinuation

Adverse events	**Standard monitoring arm (N=XX)**	**Simplified monitoring arm (N = XX)**
Participants reporting any TEAE up to 30 days after last dose, n (%) Grades 1-2, n (%) Grade 3, n (%) Grade 4, n (%)		
Participants reporting treatment-related TEAE up to 30 days after last dose, n (%) Grades 1-2, n (%) Grade 3, n (%) Grade 4, n (%)		
Serious TEAE, n (%)		
Treatment-related serious TEAE, n (%)		
Treatment discontinuation due to adverse event, n (%)		
Death, n (%)		
Adverse events *Common (>5% of study population), n (%)* Specify (list)		
Unscheduled clinic visits or phone contact, n (%)		

Table 16. Safety parameters – adverse events and treatment discontinuation, by visit type

Adverse events	**Standard monitoring arm *Phone contact* (N=XXX)**	**Standard monitoring arm *Clinic contact* (N=XXX)**	**Simplified monitoring arm *Phone contact* (N = XXX)**
Participants reporting any TEAE up to 30 days after last dose, n (%) Grades 1-2, n (%) Grade 3, n (%) Grade 4, n (%)			
Participants reporting treatment-related TEAE up to 30 days after last dose, n (%) Grades 1-2, n (%) Grade 3, n (%) Grade 4, n (%)			
Serious TEAE, n (%)			
Treatment-related serious TEAE, n (%)			
Treatment discontinuation due to adverse event, n (%)			
Death, n (%)			
Adverse events *Common (>5% of study population), n (%)* Specify (list)			

Table 17. Listing of serious adverse events

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

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

Table 18. Serious adverse events summary

SAE – event summary	Standard monitoring N=XXX	Simplified monitoring N=XXX
N of participants experiencing any treatment-emergent SAE by MedDRA SOC and Preferred Term, n (%)		
SOC (alphabetical order)		
List PT		

Table 19. Summary table for key laboratory evaluations – Standard monitoring arm

Lab parameter	N	Mean	SD	Min	Q1	Median	Q3	Max
Hb								
Baseline								
Post treatment week 12								
Change in Hb								
WBC								
Baseline								
Post treatment week 12								
Change in WBC								
Plt								
Baseline								
Post treatment week 12								
Change in plt								
ALT								
Baseline								
Post treatment week 12								
Change in ALT								
AST								
Baseline								
Post treatment week 12								
Change in AST								
Bilirubin, total								
Baseline								
Post treatment week 12								
Change in bilirubin								

Table 20. Summary table for key laboratory evaluations – Simplified monitoring arm

Lab parameter	N	Mean	SD	Min	Q1	Median	Q3	Max
Hb								
Baseline								
Post treatment week 12								
Change in Hb								
WBC								
Baseline								
Post treatment week 12								
Change in WBC								
Plt								
Baseline								
Post treatment week 12								
Change in plt								
ALT								
Baseline								
Post treatment week 12								
Change in ALT								
AST								
Baseline								
Post treatment week 12								
Change in AST								
Bilirubin, total								
Baseline								
Post treatment week 12								
Change in bilirubin								

Table 21. Laboratory evaluation

Laboratory evaluation	**Standard monitoring (N=XX)**	**Simplified monitoring (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

Reference List

1. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir-Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection. The New England journal of medicine 2018;378:354-69.
2. Asselah T, Kowdley KV, Zadeikis N, et al. Efficacy of Glecaprevir/Pibrentasvir for 8 or 12 Weeks in Patients With Hepatitis C Virus Genotype 2, 4, 5, or 6 Infection Without Cirrhosis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2018;16:417-26.
3. ICH Expert Working Group. ICH harmonised tripartite guidline: Statistical principles for clinical trials E91998.
4. Food and Drug Administration. Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry: U.S. Department of Health and Human Services 2016 November 2016.
5. EASL. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. Journal of hepatology 2015;63:237-64.