Statistical Analysis Plan for SVR4, SVR12 (Primary Analysis), and SVR24 (Final Analysis)

A Phase 2b, Multicenter, Randomized, Open-label Study to Investigate the Efficacy, Safety and Pharmacokinetics of Different Treatment Regimens of AL-335, Odalasvir, and Simeprevir in Treatment-naïve and Treatment-experienced Subjects With Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 and 6 Infection Without Cirrhosis.

Protocol 64294178HPC2001; Phase 2b

AL-335, Odalasvir, TMC435 (simeprevir)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
BMI	Body Mass Index
CFB	Change from Baseline
CI	Confidence Interval
CTP	Clinical Trial Protocol
DAA	Direct-Acting Antivirals
DBP	Diastolic Blood Pressure
DRC	Data Review Committee
ECG	Electrocardiogram
ECHO	Echocardiogram / Echocardiography
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Form
EOT	End Of Treatment
ESI	Events of Special Interest
FU	Follow-up
HCV	Hepatitis C Virus
HLT	High Level Term
HLGT	High Level Grouping Term
IA	Interim Analysis
ICH	International Conference on Harmonisation
IFN	Interferon
ITT	Intent-To-Treat
KM	Kaplan Meier
LLOQ	Lower Limit of Quantification
LOD	Limit of Detection
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
NAP	Not Applicable
ODV	Odalasvir
Peg	Pegylated
PRO	Patient Reported Outcomes
PT	Preferred Term
QD	Quaque Die, Once Daily
QTc	Corrected QT Interval
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAS	Resistance Associated Substitution
RNA	Ribonucleic Acid
RVR	Rapid Virologic Response
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SI	Standard International
SMV	Simeprevir
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SVR	Sustained Virologic Response

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TE	Treatment-emergent
VBT	Viral Breakthrough
VR	Virologic Response
vRVR	Very Rapid Virologic Response
WHO	World Health Organization

1. INTRODUCTION

This 64294178HPC2001 Statistical Analysis Plan (SAP) covers the SVR4 interim analysis, the SVR12 Primary Analysis, and the SVR24 Final Analysis. It contains definitions of analysis sets, derived variables and statistical methods for the analysis. Separate documents for mock shells and a Table of Contents are also provided. A separate SAP was written for the Data Review Committee (DRC) analyses.

Please refer to the study protocol for the background for the study.

1.1. Trial Objectives

The primary objective of this trial is to evaluate the efficacy, i.e., sustained virologic response 12 weeks after the end of treatment (SVR12), of a combination treatment with AL-335, Odalasvir (ODV), and Simeprevir (SMV) for 6 and 8 weeks in chronic HCV genotype 1, 2, 4, 5 or 6 infected subjects without cirrhosis.

Secondary Objectives

- To evaluate the safety and tolerability of a 6- and 8-week treatment regimen containing AL-335, ODV, and SMV in subjects without cirrhosis,
- To evaluate SVR4 and SVR24 of a 6- and 8-week treatment regimen containing AL-335, ODV, and SMV in subjects without cirrhosis,
- To evaluate on-treatment viral kinetics in a 6- and 8-week treatment regimen containing AL-335, ODV, and SMV in subjects without cirrhosis,
- To evaluate the incidence of on-treatment failure during a 6- and 8-week treatment regimen containing AL-335, ODV, and SMV in subjects without cirrhosis,
- To evaluate the incidence of viral relapse after an 6- and 8-week treatment regimen containing AL-335, ODV, and SMV in subjects without cirrhosis,
- To assess changes from baseline in HCV NS3/4A, NS5A, and NS5B sequence in subjects not achieving SVR,
- To evaluate the effect of the presence or absence of baseline HCV NS3/4A polymorphisms (including Q80K), NS5A polymorphisms and/or NS5B polymorphisms on treatment outcome (SVR12, on-treatment failure, viral relapse, and emergence of resistance),
- To evaluate concordance between SVR4, SVR12, and SVR24,
- To evaluate the pharmacokinetics (PK) of AL-335 (and its 2 metabolites ALS-022399 and ALS-022227; AL-335 and its metabolites ALS-022399 and ALS-022227 are further referred to as AL-335 [and metabolites]), ODV, and SMV, in plasma,
- To evaluate the relationship between the population-derived exposure parameters of AL-335 (and metabolites), ODV, and SMV (ie, area under the plasma concentration-time curve from time 0 until 24 hours post dosing [AUC24h] and predose plasma concentrations [C0h]) with SVR12 and safety,

- To explore the impact of HCV and its treatment with AL-335+ODV+SMV on the Fatigue Severity Scale (FSS) total score and the 5-level EuroQol 5-Dimension (EQ-5D-5L) Visual Analog Scale (VAS) score.

Exploratory Objectives

- To explore the effect of prior HCV treatment history, baseline host and disease related characteristics including but not limited to HCV geno/subtype, baseline HCV ribonucleic acid (RNA) level, genetic factors (eg, interleukin-28B [*IL28B*] genotype), race, sex and age on treatment outcome,
- To explore the impact of HCV and its treatment with AL-335+ODV+SMV on symptoms, functioning and health-related quality of life (HRQoL), using patient-reported outcomes (PROs), ie, EQ-5D-5L domain scores, Short Form 36 version 2 (SF-36v2) Physical Component Summary and Mental Component Summary scores, and Chronic Liver Disease Quality of Life Questionnaire – HCV (CLDQ-HCV) summary and domain scores,
- To explore the impact of HCV treatment with AL-335+ODV+SMV on occupational/employment status,
- To describe the impact of HCV treatment on medical resource utilization (MRU).

1.2. Trial Design

This is a Phase 2b, multicenter, randomized, open-label study. It consists of a 6 week screening period, followed by one of 2 treatment arms (either 6 or 8 weeks), and a 24 week follow up period. Approximately 300 subjects were planned to be randomized. The actual number of subjects randomized is 365, as described in the Protocol Amendment 4. Randomization was to one of the 2 treatment groups shown below in a 1:1 ratio:

- Arm A (N=183): AL-335 800 mg qd + ODV 25 mg qd + SMV 75 mg qd for 6 weeks
- Arm B (N=182): AL-335 800 mg qd + ODV 25 mg qd + SMV 75 mg qd for 8 weeks

The randomization is stratified by HCV treatment history (treatment naive vs treatment experienced) and HCV genotype/subtype (1a or 2 versus 1b, 4, 5, or 6). Subjects with an undefined genotype 1 subtype at screening are assigned to the 1b, 4, 5 or 6 stratification group.

If treatment extension is recommended by the DRC, the treatment duration of the arms may be extended up to a maximum of 12 weeks. Treatment extension was not recommended by the DRC however.

Further Trial Design details are available in the Protocol.

1.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is sustained virologic response 12 weeks after the end of treatment. Subjects are considered to have achieved SVR12 if the following condition has been met: HCV RNA < lower limit of quantification (LLOQ), detected or not detected 12 weeks after the end of treatment (EOT). The LLOQ for the HCV RNA COBAS® AmpliPrep/COBAS® TaqMan® Test v2.0, used in this study, is 15 IU/mL.

1.3. Statistical Hypotheses for Trial Objectives

The SVR12 rate is non-inferior in at least one treatment arm to the performance benchmark of 98% (based on historical interferon [IFN]-free, direct-acting antivirals (DAA) regimens) with a non-inferiority margin of 10%.

Statistical testing will be conducted using null hypothesis H_0: C-T≥M vs. Ha: C-T<M at a significance level of 0.05, 2-sided, where C is the historical control rate of 98%, M is the non-inferiority margin 10%, and T is the expected SVR rate in the treatment arm.
This is equivalent to the lower bound of a 95% 2-sided CI exceeding 88%.

A fixed sequence approach will be used to adjust for the multiplicity of the comparison of the SVR12 rate in the two treatment arms against the historical control. The SVR12 rate in the 6 week treatment arm will be tested first against the historical control at a significance level of 0.05, 2-sided. If non-inferiority is established then the SVR12 rate in the 8 week treatment arm will be tested against the historical control at a significance level of 0.05. 2-sided.

The fixed sequence approach will be applied only for the ITT population. Additional analyses will also be conducted in the per protocol and non-VF excluded populations without applying the fixed sequence approach.

1.4. Sample Size Justification

The description of the sizing based on 300 subjects is described below.

The sample size consideration is based on non-inferiority testing against performance benchmark 98% based on historical data (ASTRAL 1-3 studies) in an IFN-free, 2-DAA (SOF/velpatasvir [VEL]) regimen for 12 weeks of treatment. Statistical hypothesis will be tested per arm using the CI approach with the lower bound of CI excluding a predefined threshold for non-inferiority of SVR12. The SVR performance benchmark is chosen to be 98% based on ASTRAL 1-3 studies, in which, across genotypes 1-6, SVR was observed to be 98% with 95% CI: 97% to 98.8%. In a subgroup of cirrhosis (F4), the SVR was 96% with 95% CI: 92.8% to 98.4%). Non-inferiority margin 10% was determined by referencing the most recent data from the ASTRAL-2 study, where 10% non-inferiority margin was used to compare 2-DAA (SOF/VEL) to active control SOF+RBV for non-inferiority. Additionally, recent data from a 3-DAA regimen plus RBV (Abt-450/r + ombitasvir + dasabuvir + RBV) in comparison to the historical control

in a DAA with PegIFN/RBV used 10.5% non-inferiority margin for the non-inferiority testing. Therefore, a 10% non-inferiority margin was chosen for this Phase 2b study for the non-inferiority testing against historical control. Using a 2-sided 95% CI and assuming an expected SVR rate of 98% for each arm, a sample size of 150 subjects per arm will provide at least 90% power to reject the inferiority hypothesis by showing that the lower limit of the 2-sided 95% CI on the observed SVR will exceed 88% (the upper boundary of the 95% CI for the control rate minus 10%).

Note that the 65 additional subjects enrolled does not meaningfully affect the power considerations reported above to demonstrate non-inferiority of SVR12. Additionally, 182 subjects enrolled per arm (365 in total) will provide the probability to observe an adverse event (AE) with an incidence of 0.1%, 0.5%, 0.8%, and 1% of 16.6% (30.6%), 59.8% (84.0%), 76.8% (94.7%), and 83.9% (97.4%), respectively.

1.5. Randomization and Blinding

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of the 2 treatment arms in a 1:1 ratio based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The interactive voice response system (IVRS) or interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IVRS/IWRS, and will then give the relevant subject details to uniquely identify the subject. Randomized subjects in arms A and B will be stratified by HCV treatment history (treatment-naïve versus treatment-experienced) and HCV geno/subtype (genotypes 1a or 2 versus genotypes 1b, 4, 5 or 6).

Blinding is non-applicable as this is an open label study.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows and Phase Definition

Phases will be constructed as follows:

Weeks	-6	D1	D2	D3	W1	W2	W3	W4	W6	W8	W10	W12	W18	W30	W32
6 Wks	Scr.	AL-335 + ODV + SMV								Follow up					
8 Wks	Scr.	AL-335 + ODV + SMV										Follow up			

Trial phase	Start date	End date
Screening (phase 0)	Minimum of Date of signing the informed consent and	1 day before first study drug intake

Trial phase	Start date	End date
	Date of the first screening visit	
Treatment (phase 1)	Date of first study drug intake	Date of last study drug intake + 3 days
Follow-up (phase 2)	Phase 1 end date +1 day	Trial termination date (date of last contact)

Date of First Study Drug Intake: In the above computations, missing data for first study drug intake may be imputed as the date of baseline visit in (a) interim analyses and (b) preliminary (non-final) analyses.

Date of Last Study Drug Intake: In the above computations, missing data for last study drug intake may be imputed for (a) interim analyses and (b) subjects discontinuing as follows:

1) Interim analyses: Date of Last Study Drug Intake = Min (Data cutoff date, Date of baseline visit + 6 or 8 weeks depending on arm).

2) Discontinued Subjects: Date of Last Study Drug Intake =

    a. Date of the early treatment withdrawal visit, if non-missing otherwise
    b. Date of 1st available Follow-up visit – 28, if non-missing otherwise
    c. Date of last contact.

The number of days in the phase (Reldy) is defined as:

Visits on or after the reference day: Reldy = visit date – refdy+1

Visits before the reference day: Reldy = visit date – refdy

Reference date (Refdy) above is defined as:

Screening & Treatment Phases: Refdy = Date of first study drug intake (if non-missing), otherwise date of baseline visit.

Follow-up Phase: Refdy = Start Date of follow-up phase.

Actual EOT visit is defined as the last visit in the Treatment phase.

All visits (regardless of the investigated parameter) will be allocated to analysis time points based on the number of days in phase (reldy). In the below, 'Target day' is the planned reldy for the analysis time point. Actual observed relday's in the 'Time Interval' shown are assigned to the analysis time point.

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Trial phase	Target day[b]	Analysis time point (numeric version)	Analysis time point	Time interval (reldy)[a]
ARM 1				
Screening	-∞	-1	Screening	<0
Treatment phase	1	0	Baseline[a]	<=1
	2	0.2	Day 2	[2,2]
	3	0.3	Day 3	[3,5]
	8	1	Week 1	[6,12]
	15	2	Week 2	[13,19]
	22	3	Week 3	[20,26]
	29	4	Week 4	[27,36]
	43	6	Week 6	[37, + ∞]
	last visit while on study therapy or within 3 days after the day of last dose	999	EOT	
Follow-up phase	25	12	Follow-Up Week 4	[1,39]
	53	16	Follow-Up Week 8	[40,67]
	81	20	Follow-Up Week 12	[68,102]
	123	24	Follow-Up Week 18	[103,144]
	165	32	Follow-Up Week 24	[145, + ∞]
ARM 2				
Screening	-∞	-1	Screening	<0
Treatment phase	1	0	Baseline[a]	<=1
	2	0.2	Day 2	[2,2]
	3	0.3	Day 3	[3,5]
	8	1	Week 1	[6,12]
	15	2	Week 2	[13,19]
	22	3	Week 3	[20,26]
	29	4	Week 4	[27,36]
	43	6	Week 6	[37, 50]
	57	8	Week 8	[51, + ∞]
	last visit while on study therapy or within 3 days after the day of last dose	999	EOT	
Follow-up phase	25	12	Follow-Up Week 4	[1,39]
	53	16	Follow-Up Week 8	[40,67]
	81	20	Follow-Up Week 12	[68,102]
	123	24	Follow-Up Week 18	[103,144]
	165	32	Follow-Up Week 24	[145, + ∞]

[a] If the reldy of the baseline value closest to the target day is less than 0, only the record closest to the target day will be retained in the Analysis Data Model (ADaM) dataset, otherwise only the record(s) with reldy 1 will be kept.

[b] Target day in follow up phase equals target day in the protocol minus 3 days due to definition of start of follow-up phase.

Note: In case of treatment extension recommended by the DRC, a supplementary table to the above will be added.

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If two visits fall within the same interval, the last measurement within the interval will be used for descriptive statistics/tabulations per time point and graphics in order to have only one evaluation per subject per analysis time point. If two measurements occur on the same day, the measurement with highest sequence number will be used. Listings will include all values.

2.2. Pooling Algorithm for Analysis Centers

No pooling of analysis sub-centers will be performed in this study.

2.3. Analysis Sets

Intent-to-treat (ITT) population: All randomized subjects who took at least 1 dose of investigational medication.

Non-VF excluded population: all ITT subjects excluding the subjects who did not achieve SVR12 due to reasons other than virologic failure, including subjects with missing data at the SVR12 time point and subjects who discontinued all treatment prematurely (e.g. AE or withdrawal of consent).

The *per-protocol (PP) population* is the set of all subjects in the ITT population with the exclusion of any subjects deemed to have a major protocol deviation that may affect the assessment of efficacy. The major protocol deviations that may affect the assessment of efficacy will be identified prior to database lock. Specific details are provided in Appendix 5.

All analyses will be done on the ITT population. Selected efficacy analyses including on the primary efficacy endpoint will be done also on the Non-VF excluded population and the per protocol population. These are to be specified prior to Database Lock. Additional analyses on the per protocol population may be produced in case of >10% of subjects with a major protocol deviation that may affect the assessment of efficacy. Demographic and baseline characteristics specifically should be done on the ITT, per protocol and non-VF excluded populations.

Prior to each database lock, an Excel spreadsheet listing all major protocol deviations will be produced. This will undergo medical review according to the major PD criteria list in Appendix 5, and a new column will be added indicating if each major PD will lead to that subject being excluded from the per protocol population.

2.4. Definition of Subgroups

The following subgroups will be investigated for efficacy, combinations of more than one subgroup may also be done. In case subgroup categories are smaller than 10 subjects within a treatment arm, subgroup categories might be combined.

- Prior HCV treatment (Naive, Experienced)
- Baseline HCV RNA (<6,000,000 IU/mL; ≥6,000,000 IU/mL)

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- IL28B genotype (CC, CT, TT); and also (CC, non-CC)
- HCV geno/subtype (1a [Overall, with Q80K at baseline, without Q80K at baseline], 1b, 1other, 2, 4, 5, 6); and also by stratification factor (genotypes 1a or 2 versus genotypes 1b, 1other, 4, 5 or 6)
- Gender (male, female)
- Race (Caucasian, Black or African American, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Age category [≤45; >45-≤65; >65]
- BMI [<25; 25-<30; ≥30]
- Fibrosis stage (F0/1; F2; F3) (investigator determination)
- Fibrosis stage (non-F3; F3) (criteria determination)
- HCV RNA at early time points: Day 3, Day 7, Week 2, Week 4: (<15IU/mL not detected, <15IU/mL detected, <15 IU/mL not detected or detected) (Week 2 and Week 4 not to be done for the efficacy endpoints of HCV RNA at Week 2 and at Week 4)
- Presence of NS3/4A, NS5A and/or NS5B baseline polymorphisms (yes, no) (refer to virology section)

In addition, the above subgroups for efficacy (except for HCV geno/subtype) should be further evaluated split by HCV geno/subtype (1a,1b, 1other, 2, 4, 5, 6). Also evaluate these efficacy subgroups for each subtype within an HCV genotype. Categories with a small number of subjects might be combined. Care should be taken in interpreting any subgroups with a small number of subjects.

Subgroups for PRO will include:

- SVR12 (yes, no)
- BMI [<25; 25-<30; ≥30]
- Gender (male, female)
- Age category [≤45; >45-≤65; >65]
- Prior HCV treatment history (Naive, Experienced)
- HCV geno/subtype (genotypes 1a or 2 versus genotypes 1b, 1other, 4, 5 or 6)

The following subgroups will be investigated for safety:

- Prior HCV treatment (Naive, Experienced)
- Age category [≤45; >45-≤65; >65]
- Gender (male, female)
- Race (Caucasian, Black or African American, Asian, Other)
- BMI [<25; 25-<30; ≥30]

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3. SUBJECT INFORMATION

3.1. Demographics and Baseline Characteristics

Descriptive statistics or tabulation will be provided, in addition to listings, for the following parameters:

Demographic parameters

- Gender
- Age at screening (years)
- Age at screening (years, categories: ≤45; >45 - ≤65; >65)
- Race (American Indian or Alaska Native, Asian, Black or African American, Caucasian, Native Hawaiian or Other Pacific Islander, Other, Unknown, Not Reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Not Latino)
- Weight at baseline (kg)
- BMI at baseline = weight (at baseline, in kg)/ (height (at screening, in meters))^2, rounded to 1 decimal (although available in the raw data, BMI will be recalculated from weight and height)
- BMI at baseline (categories: <25, 25-<30, ≥30)

Baseline disease characteristics

- baseline HCV RNA (original and $\log_{10}$ units)
- baseline HCV RNA categories (<6,000,000IU/mL; ≥6,000,000 IU/mL)
- HCV geno/subtype: 1a, 1b, 1other, 2, 4, 5, 6. For 1other, 2, 4, 5, 6 show also a breakdown of each subtype.
- IL28B genotype (CC, CT, TT); and also (CC, non-CC)
- For subjects with Fibroscan Results, Fibrosis Result (kPa) summary statistics
- For all subjects, Metavir Fibrosis stage (F0/F1, F2, F3) (investigator determination)
- For all subjects, Metavir Fibrosis stage (non-F3, F3) (criteria determination)
- Prior HCV treatment (Treatment-naive, Treatment-experienced)
- Mode of HCV infection (Blood Transfusion, Intravenously Injectable Drug Use, Occupational Exposure, Mother To Child Transmission, Heterosexual Contact, MSM, Hemophilia-Associated Injections, Other)
- Duration of HCV infection (years) (= (baseline date – date of HCV infection + 1)/365.25, rounded to 1 decimal).
- Time since diagnosis (years) (= (baseline date – date of diagnosis + 1)/365.25, rounded to 1 decimal)

3.1.1. Liver Fibrosis Staging Parameters

Documentation of Absence of Cirrhosis:

All subjects will be tested (based on Fibroscan, Biopsy, or both) to determine the liver fibrosis stage and to document an absence of cirrhosis as part of eligibility criteria. Presence or absence of cirrhosis (Yes, No) will be computed as positive if either the Fibroscan or Biopsy results are positive for cirrhosis. Liver fibrosis staging by either Fibroscan and biopsy are determined by the investigator and recorded in the CRF. As an additional criteria based determination, subjects with liver fibrosis stage F3 will be selected as those with a Fibroscan result of >9.5 to ≤12.5 kPa, and also those with an F3 determination where only the biopsy was performed.

Any subjects in the study with cirrhosis will be considered a major protocol deviation.

Liver Staging Parameters

All subjects will have a Fibroscan if feasible. Subjects for whom Fibroscan is not feasible will have a liver biopsy. Liver staging data will be summarized.

3.1.2. Definition of Prior HCV Treatment

Subjects with chronic HCV infection in this study will be either Treatment-naïve or Treatment-experienced, defined as follows:

- Treatment-naives: Subjects who have never received treatment with any approved or investigational drug (including DAA's, IFN-based treatments, and vaccines) for chronic HCV infection.
- Treatment-experienced: Subjects who have received at least one previous course of IFN (Peg or non-Peg) with or without RBV but have never received treatment including an approved or investigational HCV DAA.

3.2. Disposition Information

Tabulations will be provided for the following disposition information:

- Number of subjects screened, randomized, randomized and not treated, randomized and treated
- Number of subjects with a visit per analysis time point
- Number of subjects prematurely discontinuing any single study medication and the reason for discontinuation (obtained from the end of treatment page of the electronic case report form [eCRF])

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- Number of subjects prematurely discontinuing the trial and the reason for discontinuation. Reasons for discontinuation are obtained from the end of trial page of the eCRF.

3.3. Extent of Exposure

Treatment duration (in weeks) is derived as follows for each of the three drugs (AL-335, Odalasvir, SMV):

(Last date of exposure – first date of exposure + 1) / 7

Note: treatment interruptions will not be taken into account for the above definition.

Treatment duration and total dose received will be summarized descriptively by treatment arm. Treatment duration for subjects who did not complete treatment will also be summarized descriptively by treatment arm.

3.4. Treatment Adherence

For each of the three drugs (AL-335, Odalasvir, SMV), the actual amount (actual dose over actual treatment duration) of study drug relative to the planned cumulative total dose (planned dose over planned duration) will be summarized.

For each drug, the number (%) of subjects with ≤3 and >3 consecutive days of dose interruption will be tabulated. The number of subjects without a dose interruption will also be tabulated. Summary statistics for the total number of days of dose interruption for subjects with at least one day of dose interruption will also be tabulated. Further, for each drug, the number (%) of subjects with ≤3, 4 - ≤6, and > 6 cumulative days of dose interruption will be tabulated.

In addition, the percentage of drug that was used based on pill count will also be summarized: 100 x (amount dispensed – amount returned)/amount dispensed.

3.5. Protocol Deviations

All major protocol deviations will be tabulated. Additionally all protocol deviations (major and minor) will be listed. Major protocol deviations that may affect the assessment of efficacy will be flagged in the listing.

3.6. Prior and Concomitant Medications

Prior medications will be tabulated by treatment arm. Concomitant medication are allocated to phases based on their start date. If the concomitant medication starts in a specific phase, then the concomitant medication is allocated to that phase. A concomitant medication can be allocated to more than one phase. Concomitant medications will be tabulated by treatment arm and phase.

Incomplete dates (i.e. day and/or month and/or year missing):

- In case of a partial start date, the therapies are allocated to the phases using the available partial information, no imputation is done. If, for instance, for a therapy start date only month and year is available, these data are compared with the month and year info of the phases.

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- In case of a completely missing start date, the therapy is considered as having started before the trial. In case of a completely missing end date, the therapy is considered as ongoing at the end of the trial.

3.7. Medical History

Frequency tabulations of medical history will be provided.

3.8. Treatment Extension

If treatment extension is recommended by the DRC, the treatment duration of the arms may be extended up to a maximum of 12 weeks (see Section 1.2). In this event a table will be foreseen to show the number of subjects per arm with a treatment extension.

4. EFFICACY

4.1. Analysis Specifications

4.1.1. Level of Significance

See Section 1.3

4.1.2. Data Handling Rules

Plasma HCV RNA will be determined using an in vitro nucleic acid amplification test for the quantification of HCV RNA in human plasma using a sensitive assay (COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0, lower limit of quantification [LLOQ] = limit of detection [LOD] = 15 IU/mL). HCV RNA determination will be performed at a central laboratory.

Before performing continuous analyses or log transformations, HCV RNA results of '<LLOQ IU/mL HCV RNA DETECTED' will be converted to LLOQ-1 IU/mL and 'HCV RNA NOT DETECTED' will be converted to LOD-2 IU/mL.

Note: We subtract 2 from the LOD to distinguish between '<LLOQ IU/mL HCV RNA DETECTED' and '<HCV RNA NOT DETECTED' in all cases, as the LLOQ could equal the LOD.

4.1.3. SVR4 time point efficacy analysis

For the interim analysis when all subjects have reached the SVR4 time point or discontinued earlier, for subjects not yet reaching the time point of SVRx (where x=8, 12, 18, or 24), SVRx will not be evaluated. Further, for secondary efficacy endpoint definitions (Section 4.3) which include a statement on achieving/not achieving SVR12, this statement should be disregarded for such subjects not yet reaching the time point of SVR12 in the SVR4 analysis (a similar approach was taken for the DRC SAP).

In the SVR4 analysis, subjects should not be recorded as being a failure under 'Missing at time point of SVR12'. However, the viral relapse evaluation should still be done, and will be relative to the Week 12 Follow-up time point. So, for example, a subject not yet

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reaching the time point of SVR12 could have achieved SVR4 but also have a viral relapse which occurred after the SVR4 time point. Late viral relapse is not evaluable for subjects not yet reaching the time point of SVR12.

Additionally, it should be noted that viral breakthrough is a stopping rule for this study.

4.2. Primary Efficacy Endpoint

The primary efficacy endpoint is sustained virologic response 12 weeks after the end of actual treatment, as defined below.

4.2.1. Definition

SVR12 is defined as follows:

- 1= success:
    - at the timepoint of SVR
        - HCV RNA Not Detected or
        - HCV RNA <LLOQ Detected and
            - the sample is a confirmation* sample or
            - the sample is the last available HCV RNA measurement or
            - at the next available measurement, HCV RNA Not Detected or HCV RNA <LLOQ Detected
        - ≥ LLOQ quantifiable and
            - the sample is not a confirmatory sample* and
            - not the last available measurement in the study and
            - a next measurement is available and HCV RNA Not Detected or HCV RNA <LLOQ Detected for this next measurement

- 0= failure: otherwise

* Confirmed means that the criterion should be fulfilled at 2 or more consecutive time points or at the last observed time point.

Add 'The LLOQ for the HCV RNA COBAS® AmpliPrep/COBAS® TaqMan® Test v2.0, used in this study, is 15 IU/mL.' as a footnote.

Timepoint of SVR:

- 12 weeks after the actual EOT (Select the measurement in the SVR12 analysis window. If >1 measurements are present in this window then select the one latest in time.)
- or, if not available, the first available measurement at least 12 weeks after the actual EOT (i.e. the first available measurement after the SVR12 analysis window)
- or, if not available (i.e. no measurement at least 12 weeks after the actual EOT), the subject is considered a failure. Note: For the SVR4 analysis, if

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the time point of SVRx (x=8, 12, 18 or 24) has not been reached then those SVR time points will not be evaluated.

4.2.2. Primary Efficacy Analysis Method

Statistical testing will be conducted using null hypothesis H_0: C-T≥M vs. Ha: C-T<M at a significance level of 0.05, 2-sided, where C is the historical control rate of 98%, M is the non-inferiority margin 10%, and T is the expected SVR rate in the treatment arm. This is equivalent to the lower bound of a 95% 2-sided CI exceeding 88%. An exact 95% 2-sided Clopper-Pearson CI will be calculated.

A fixed sequence approach will be used to adjust for the multiplicity of the comparison of the SVR12 rate in the two treatment arms against the historical control. The SVR12 rate in the 6 week treatment arm will be tested first against the historical control at a significance level of 0.05, 2-sided. If non-inferiority is established then the SVR12 rate in the 8 week treatment arm will be tested against the historical control at a significance level of 0.05, 2-sided.

The fixed sequence approach will be applied only for the ITT population. Additional analyses will also be conducted in the per protocol and non-VF excluded populations without applying the fixed sequence approach.

4.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- **Evaluated during the treatment phase includes:**

  - The proportion of subjects with On-Treatment Virologic Response at all available treatment timepoints (HCV RNA Not Detected, HCV RNA Not Detected or HCV RNA <LLOQ Detected);
  - The proportion of subjects with viral breakthrough;
  - The proportion of subjects with on-treatment failure

- **Evaluated during the follow up phase includes:**

  - The proportion of subjects with SVR4;
  - The proportion of subjects with SVR8;
  - The proportion of subjects with SVR18;
  - The proportion of subjects with SVR24;
  - The proportion of subjects with post-treatment failure;
  - The proportion of subjects with viral relapse;
  - The proportion of subjects with late viral relapse (relapse at a later time point than SVR12);
  - Time from EOT to viral relapse

4.3.1. Definitions

Evaluated in the treatment phase:

On-Treatment Virologic Response is defined as follows:

- 0 = HCV RNA result not satisfying a specified threshold
- 1 = HCV RNA result satisfying a specified threshold

The following thresholds will be considered at any time point:

- "HCV RNA Not Detected"
- "HCV RNA Not Detected or HCV RNA <LLOQ Detected"

Note: virologic response will always be calculated as on-treatment response; therefore, the denominator will only include those subjects with valid on-treatment HCV RNA per analysis time point.

Other definitions of virologic response:

vRVR (Very Rapid Virologic Response): HCV RNA Not Detected at Week 2 of treatment (the denominator for the proportion of subjects with vRVR will be the number of subjects who have a non-missing Week 2 measurement while on therapy (or within 3 days of the date of last dose))

RVR (Rapid Virologic Response): HCV RNA Not Detected at Week 4 of treatment (the denominator for the proportion of subjects with RVR will be the number of subjects who have a non-missing Week 4 measurement while on therapy (or within 3 days of the date of last dose))

On-Treatment failure is defined as subjects who did not achieve SVR12 with confirmed HCV RNA ≥LLOQ at EOT or for which the last available on-treatment measurement is HCV RNA ≥LLOQ and for which no follow-up measurements are available, or subjects with viral breakthrough (see below).

> *Viral breakthrough* is defined as subjects with a confirmed increase while on study therapy of > 1 $\log_{10}$ IU/mL in HCV RNA level from the nadir (= lowest value measured in between baseline and current value) when the lowest value reached is >=LLOQ, or a confirmed HCV RNA level of > 100 IU/mL while on study therapy in subjects who previously achieved HCV RNA Not Detected or HCV RNA <LLOQ Detected. A subject with viral breakthrough does not subsequently achieve SVR12.
> Viral breakthrough is a type of on-treatment failure.
> In this study, viral breakthrough is a treatment stopping rule, meaning all study drugs should be discontinued.
>
> The proportion of subjects with a viral breakthrough is defined as follows:

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- 0 = subject has not had a viral breakthrough (see definition above) up to the considered time point
- 1 = subject has a viral breakthrough at the considered timepoint or has had a viral breakthrough before (regardless of the HCV RNA result at the considered time point)

Confirmed means that the criterion should be fulfilled at 2 or more consecutive time points or at the last observed time point.

Evaluated in the treatment and follow-up phases:

Failure: subjects not achieving SVR12 including:

- In the treatment phase: On-treatment failure (see above)
- In the follow-up phase: Post-treatment failure, includes subjects with:
    - Viral relapse after completed treatment
    - Viral relapse after premature discontinuation of treatment
    - Missing HCV RNA at timepoint of SVR12.

Type of failure: if more than 1 type of failure occurs, the order as presented below should be respected:

1) Viral Relapse
2) Viral breakthrough
3) Confirmed HCV RNA ≥LLOQ at EOT
4) Missing at timepoint of SVR12

Evaluated in the follow-up phase:

SVR4, SVR8, SVR18 and SVR24 are defined similarly as SVR12 but with 4, 8, 18 and 24 weeks instead of 12 weeks. Note: For the SVR4 analysis, if the time point of SVRx (x=8, 12, 18, or 24) has not been reached then those SVR time points will not be evaluated.

In addition, for SVR24, the timepoint of SVR is defined as follows:

- 24 weeks after the actual EOT (Select the measurement in the SVR24 analysis window. If >1 measurements are present in this window then select the one latest in time.)
- or, if not available, the first available measurement at least 24 weeks after the actual EOT (i.e. the first available measurement after the SVR24 analysis window)
- or, if not available, the last measurement available in the SVR18 analysis window, on condition that the time point of SVR24 has been reached
- or, if not available, the last measurement available in the SVR12 analysis window, on condition that the time point of SVR24 has been reached
- or, if not available, the subject is considered to have not achieved SVR24. Note: For the SVR4 and SVR12 analyses if the time point of SVR24 has not been reached then SVR24 will not be evaluated.

For SVR18, the timepoint of SVR is defined as follows:

- 18 weeks after the actual EOT (Select the measurement in the SVR18 analysis window. If >1 measurements are present in this window then select the one latest in time.)
- or, if not available, the first available measurement at least 18 weeks after the actual EOT (i.e. the first available measurement after the SVR18 analysis window)
- or, if not available, the last measurement available in the SVR12 analysis window, on condition that the time point of SVR18 has been reached
- or, if not available, the subject is considered to have not achieved SVR18. Note: For the SVR4 and SVR12 analyses if the time point of SVR18 has not been reached then SVR18 will not be evaluated.

Viral relapse is defined as follows:

1 = viral relapse

a) Subject is not achieving SVR12 (see definition in 4.2.1)

and

b) Subject is not an on-treatment failure (see above)

and

c) Post treatment HCV RNA measurement fulfill one the following conditions:

- at least 2 consecutive measurements are ≥ LLOQ IU/mL quantifiable

or

- the last available measurement is ≥ LLOQ IU/mL quantifiable

0 = no viral relapse: at least one post-treatment measurement available and not a viral relapse

2 = no post-treatment HCV RNA measurements available

Note: viral relapse will only be assessed for those subjects with no on-treatment failure. The denominator will only include those subjects with values 0 and 1.

Late Viral relapse is defined as follows:

1 = late viral relapse

a) Subject is achieving SVR12 (see definition in 4.2.1)

and

b) Post treatment HCV RNA measurement beyond the SVR12 time point fulfill one the following conditions:

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- at least 2 consecutive measurements are ≥ LLOQ IU/mL quantifiable

or

- the last available measurement is ≥ LLOQ IU/mL quantifiable

0 = no late viral relapse: at least one measurement after the time point of SVR12 available and not a late viral relapse.

2 =no measurement after time point of SVR12 available.

Note: late viral relapse will only be assessed for those subjects with no on-treatment failure and no viral relapse. The denominator will only include those subjects with values 0 and 1.

Time to virologic response is defined as the number of days since the first day of medication intake until the first day that the threshold was achieved. The following thresholds are considered:
- HCV RNA Not Detected
- HCV RNA <LLOQ (Detected or Not Detected)

4.3.2. Analysis Methods

All analyses will be done on the ITT population. Selected efficacy analyses will be done also on the Non-VF excluded population. These are to be specified prior to Database Lock.

The difference in SVR12 rates between the 6 week and 8 week treatment arms (6 weeks – 8 weeks) will be calculated, together with a 2-sided 95% CI for the difference, calculated using a normal approximation with continuity correction.

SVR4, SVR8, SVR18 and SVR24 rates will additionally be calculated.

Descriptive statistics (n, mean (se), median, interquartile ranges and ranges) per time point for the continuous parameters (actual values and change from baseline in $\log_{10}$ HCV RNA).

Tabulations (numbers and proportions and 95% CI) per treatment group and time point for the categorical parameters will be provided.

Cross-tabulations of HCV RNA for SVR4 by SVR12, and for SVR12 by SVR24 will be provided.

Subgroup analyses as defined in section 2.4 and combination of these factors will be performed for the following efficacy endpoints: SVR12, SVR4, HCV RNA at Week 2, HCV RNA at Week 4, HCV RNA at EOT, viral breakthrough, viral relapse, and a 95% CI will be constructed around the different subgroups. Viral relapse will also be presented by treatment completion.

In addition, the reason for success/failure will be explored by type of failure and completion of study treatment.

A 'time to viral relapse' analysis will be conducted if at least 5 subjects in total have an event. Kaplan-Meier estimates per arm will be calculated. In addition, Kaplan-Meier curves per arm will be constructed.

4.3.3. Treatment Stopping Rules

All study drugs will be discontinued for any subject with viral breakthrough (see the definition in Section 4.3.1). Additionally an individual subject may stop one or all study drugs if a specific toxicity is met (see Section 9.8.6 of the protocol for full details).

The occurrence of any one of the following treatment-emergent events in any ongoing study using ODV at therapeutic doses:

- 2nd degree Mobitz Type 2 or 3rd degree heart block;
- drop in EF by ≥10 points with absolute EF <50%;
- a cardiac event that is serious, severe or life-threatening;

will lead to stop of recruitment and dosing in all subjects in the current study if adjudicated by the DRC to be at least possibly related to the study regimen. Such event(s) will be reported to the sponsor medical monitor within 24 hours. Upon this notification, a safety assessment of the event by the DRC will take place within 48 hours and the outcome of the assessment and its associated action towards the study will be reported to Health Authorities and Ethics Committees in compliance with safety reporting regulations, as applicable.

5. VIROLOGY

5.1. Virology Assessments

5.1.1. Viral strain typing

The HCV geno/subtype is determined at screening for study eligibility/stratification using the HCV LiPA v2.0 test and in case no result is obtained the NS5B-based test is used as reflex. In addition, the HCV geno/subtype is determined at baseline for efficacy and virology analyses using the NS5B-based test. In case no result at baseline is obtained, the screening results are used for efficacy and virology analyses.

5.1.2. Viral sequencing

The HCV NS3/4A, NS5A and NS5B regions are sequenced using Next Generation Sequencing (1% read frequency cut-off) in all subjects at baseline and post-baseline in subjects not achieving SVR, focusing on the time of virologic failure and the end of study.

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5.2. Virology Definitions

- **Baseline polymorphisms** are defined as amino acid differences from a HCV reference strain with a read frequency ≥15%. The reference strains used for the genotypes included in the study are shown below.

Genotype	Reference Strain (GenBank Accession ID)
1a	H77 (NC_004102)
1b	Con1 (AJ238799)
Other genotype 1 subtypes or subtype unknown	H77 (NC_004102)
2	JFH-1 (AB047639)
4	ED43 (GU814265)
5	SA13 (AF064490)
6	EUHK2 (Y12083)

- **Treatment-emergent substitutions** are defined as amino acids detected post-baseline ≥15% and not detected (i.e. <1%) at baseline.
- **Treatment-enriched substitutions** are amino acids detected at baseline with a read frequency ≥1% and <15%, and with an increase in read frequency of at least 15% post-baseline.
- **Return to Baseline** is defined as a treatment-emergent substitution which is no longer detected (ie <1%) at end of study, but instead the baseline amino acid is observed.
- **Resistance-associated substitutions (RASs)** are amino acids present at baseline or post-baseline at the positions of interest (see below) in the sequenced regions which are known to confer resistance to one of the drugs. Of note, not all amino acids at the positions of interest are RASs.
- **HCV NS3 positions of interest**:
  - List of 18 positions associated with resistance to NS3/4A protease inhibitors: 36, 41, 43, 54, 55, 80, 107, 122, 132, 138, 155, 156, 158, 168, 169, 170, 174 and 175
  - List of 8 positions associated with resistance to SMV: 43, 80, 122, 132, 155, 156, 168 and 170
- **HCV NS5A positions of interest**:
  - List of 18 positions associated with resistance to NS5A inhibitors: 6, 21, 23, 24, 28, 29, 30, 31, 32, 37, 38, 52, 54, 58, 62, 64, 92, and 93
  - List of 8 position associated with resistance to ODV: 28, 29, 30, 31, 32, 58, 92, and 93
- **HCV NS5B positions of interest**:
  - List of 9 positions associated with resistance to NS5B polymerase inhibitors: 96, 142, 159, 223, 226, 282, 316, 320, and 321
- **Virologic Failure (VF)**: subjects not achieving SVR12 for virologic reasons, including on-treatment failure, i.e. viral breakthrough (VBT) or confirmed HCV RNA ≥LLOQ at end of treatment (EOT) for subjects who completed treatment, and viral relapse.
- **Non-VF excluded population:** ITT population excluding the subjects who did not achieve SVR12 due to reasons other than VF, including subjects with missing data at

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the SVR12 time point and subjects who discontinued all treatment prematurely (eg AE or withdrawal of consent).

5.3. Virology Time Points and Samples

- **Baseline**: the sample taken at baseline or, if not available, the sample taken at screening is used.
- **Time of (virologic) failure**: the sample taken at virologic failure (ie at VBT, at actual EOT for subjects with confirmed HCV RNA ≥LLOQ at EOT or at relapse) with sequencing data available or, if not available, the first available sample after virologic failure with sequencing data available is used.
- **End of Study (EOS)**: the last available sample with sequencing data available in the study is used.

5.4. Virology Analyses

5.4.1. HCV geno/subtype analyses

The number of subjects by HCV geno/subtype for study analyses will be tabulated in frequency outputs (n, %). In addition, a cross-tabulation will compare the HCV geno/subtypes determined at screening (LiPA with NS5B-based reflex) versus baseline (NS5B-based test).

5.4.2. Resistance analyses

5.4.2.1. Baseline

The prevalence of baseline polymorphisms, ie the number of subjects with baseline polymorphism, will be tabulated in frequency outputs (n, %) and the amino acid changes from reference at baseline will be listed for all subjects using a 1% cut-off. In addition, subgroup analyses by the presence of baseline polymorphisms will be tabulated to evaluate the impact on response.

5.4.2.2. Post-Baseline

Time of Failure

For subjects with failure, the incidence of treatment-emergent and treatment-enriched substitutions will be tabulated (if N ≥10) in frequency outputs (n, %) and the amino acid changes from reference will be listed for all subjects with post-baseline sequencing data using a 1% cut-off.

End of Study

The return to baseline at end of study for the subjects with failure and treatment-emergent substitutions at time of failure will be tabulated (if N≥10) in frequency outputs (n, %) as well as the treatment-emergent substitutions at end of study in the subjects who did not return to baseline.

5.4.2.3. Over the Study Period

For the subjects with failure HCV RNA profiles and listings including the reason of failure, relevant baseline disease and demographic characteristics, all amino acid changes

from reference at baseline, time of failure and end of study using a 1% cut-off as well as the sequencing follow-up time will be generated. Similar HCV RNA profiles and listings will be generated for subjects with a late viral relapse.

Kaplan-Meier graphs and descriptive statistics will be calculated (if N≥5) to evaluate the time to return to baseline sequence in subjects with failure and treatment-emergent substitutions at time of failure.

6. SAFETY

Unless otherwise specified, all safety analysis will use ITT.

6.1. Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs will be included in the analysis.

6.1.1. Definitions

For the purpose of the analysis, AEs are allocated to the study phase. The phase allocation of AEs consists of a combination of two steps:

- AEs are allocated to phases
- Overlapping/consecutive AEs are combined

This is detailed in Appendix 1.

Treatment-Emergent AE(TEAE)

Treatment-emergent AEs are AEs that start on or after the first dose or that are a consequence of a pre-existing condition that has worsened since baseline.

AE duration calculation

Duration is calculated as End date – Start date + 1.

Prevalence

The prevalence is defined as the total number of events that occurred (not necessarily new occurrence) in a given time period. The denominator for calculating prevalence and comparable incidence (new occurrences during the same time period) rates will be based on the number of subjects still on treatment at the start of the time period. Note that prevalence counts any AEs regardless whether they are new or sustained from onset prior to the start of the current time interval while comparable incidence refers to new AEs only reported in the current time interval.

Anticipated AEs

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen. For the purposes of this study the following groups of events will be considered anticipated events:

- Progression of underlying chronic hepatitis C:
  a. Cirrhosis and its complications:
     - Portal hypertension
     - Esophageal varices
- Elderly population (age >65years)
  - Motor vehicle accident
  - Hip fracture
  - Carcinomas (other than hepatic related carcinomas including hepatocellular carcinomas)

6.1.2. Analysis Methods

All AE analyses will be performed over the treatment and follow-up phases using incidence tabulations (n and %). (i.e., Separate analyses will not be prepared for treatment and follow-up phases, rather all AE's occurring during either the treatment or follow-up phase will be tabulated together, without regard as to which phase they were in).

Only treatment-emergent AEs will be analyzed.

6.1.2.1. General AE Profile

To get an overall understand of safety profile, a brief summary table using frequency and percentage will be provided. It will include below information:

- Any AEs
- AEs by WHO toxicity
- Treatment related AEs
- AEs with fatal outcome
- Serious AEs (SAEs)
- AEs leading to permanent stop of study medication
- Relation to HCV infection

The incidence and the incidence rate of treatment-emergent AEs by system organ class (SOC) and preferred term (PT) will be calculated. The incidence rate for treatment-emergent AEs in at least 5% of subjects will be tabulated separately.

The incidence and incidence rate of AEs with WHO toxicity grade 3 or 4, SAEs, treatment related AEs, AE with fatal outcome and AEs leading to permanent stop of study medication will also be tabulated by SOC and PT.

The incidence and comparable prevalence rate per 2-week time interval for any AEs will be tabulated and plotted to evaluate the safety profile over time (treatment and follow-up phase).

Treatment-emergent AEs will be considered for below subgroup analysis by SOC and PT:

- Age (≤ 45, > 45 - ≤ 65 and > 65 yrs)
- Sex
- Race
- BMI (< 25 kg/m^2, >= 25 - < 30 kg/m^2 and >= 30 kg/m^2)

A table will be provided for subjects who met study stopping rules, such as 2nd degree Mobitz Type 2 or 3rd degree heart block, cardiac event that is serious, severe or life-threatening. Drop in LVEF for Echocardiographic(ECHO) by ≥10 points with absolute LVEF <50% will be presented too.

Anticipated AEs (serious vs non-serious) will be presented using incidence. Summary of demographics, concomitant medication class and time to onset for the patients who had anticipated AEs will be provided as well.

Listings will be provided for all subjects with any AEs, subjects with serious AEs (SAEs), subjects who had AEs leading to death, subjects had AEs leading to permanent stop of any drug among AL-335, ODV and SMV, and subjects who had grade 3 or 4 AEs. Also AE listing will be provided for the events which meet study stopping rules. Anticipated AEs will be listed as well. Listings should be provided for each phase including screening.

6.1.2.2. Events of Special/Clinical Interest

Events of special interest (ESI) and events of clinical interest (ECI) are clinical or nonclinical findings that may suggest potential safety issues or toxicities in humans. Events as ESIs and ECIs that require special collection and/or reporting are specified by

an interdisciplinary team led by the clinical team via MedDRA term or Standardised MedDRA Queries (SMQ) term grouping exercise.

The events of interest are listed in below table. Please refer the search terms related to MedDRA and MedDRA SMQ in Appendix 2A and 2B which will be finalized prior to database lock.

	Events of Interest	Defined by
Events of special interest	Cardiac Events	SMQ
	Increased Bilirubin	MedDRA PTs
Events of clinical interest	Rash (all type)	MedDRA HLTs, PTs, SMQ
	Photosensitivity conditions	MedDRA PTs
	Pruritus	MedDRA HLT

A brief summary table will be provided for the number of subjects with events of interests in treatment and follow-up phases. Subgroup evaluation will also be performed for the brief summary results.

The incidence rates of the events of interest by WHO toxicity grades, treatment relationship, with fatal outcome, as a SAE, leading to permanent stop of study medications will be generated in a summary table using frequency and percentage.

The incidence rates will be summarized by PT for each event of interest, and it will be summarized for AEs with worst toxicity grade of 3 or 4 separately as well.

Time to the first occurrence of the events of interest will be summarized and described using Kaplan Meier (KM) Curve also.

The incidence and prevalence per 2-week time interval will be summarized and plotted over the treatment and follow-up phase.

Subgroup analysis will be conducted for each event of interest by PT. Subgroup evaluation includes:

- Age (≤ 45, > 45 - ≤ 65 and > 65)
- Sex
- Race
- BMI (< 25 kg/m^2, $>= 25$ - < 30 kg/m^2 and $>= 30$ kg/m^2)

Additionally, for cardiac events, below graphs will be considered:

- Spaghetti plots of selected laboratory parameters (creatine kinase and BNP) by treatment group over time for the patients who had cardiac events
- Bar graphs of the worst toxicity grade of cardiac events over time by treatment group

Listings will be provided for the subjects with events of special/clinical Interest. The separate listings for subjects with event of interest of cardiac event and rash from SMQ will be provided.

6.2. Clinical Laboratory Tests

Clinical Lab data are collected at the Screening, Baseline, Week 1, Week 2, Week 4, EOT, FU Week 4, Week 12, and Week 24. Blood samples for serum chemistry and hematology and urine sample for urinalysis are collected.
Baseline is the Day 1 measurement, if available. If not available the Screening value will be used.

All analyses will be done on standardized international (SI)-converted values.

6.2.1. Definitions

World Health Organization (WHO) Toxicity Grade

Grades assigned by the central lab will be used. In case no toxicity grades are defined for a test, the abnormalities (above/below normal range) will be used. The abnormalities 'abnormally low' and 'abnormally high' are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally high value post- baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%). If, for a specific test, the grading list provides distinct limits for abnormally low (=hypo) values as well as for abnormally high (=hyper) values, this test should be repeated for hyper and hypo limits separately in cross-tabulations and in the ADaM database.

For the grades, no distinction will be made between test results of samples obtained under fasting and under non-fasting conditions: in case limits under fasting and non-fasting conditions differ, the limits of the conditions (fasting/non-fasting) of scheduled visits as planned in the clinical trial protocol will always be used, also for samples obtained under a different condition (e.g. samples of withdrawal visits).

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Treatment-emergent

An abnormality (toxicity grade or abnormality based on normal ranges) will be considered treatment-emergent if it is worse than the baseline. If the baseline is missing, the abnormality is always considered as treatment-emergent. A shift from 'abnormally low' at baseline to 'abnormally high' post baseline (or vice versa) is also treatment-emergent.

DAIDS coding for CK

Creatine Kinase (CK) was not planned to be coded in the protocol. However, for analysis purpose it will be coded using DAIDS (version 2.0) as below:
Grade 1: 3 to < 6 x ULN
Grade 2: 6 to < 10 x ULN
Grade 3: 10 to < 20 x ULN
Grade 4: ≥ 20 x ULN

6.2.2. Analysis Methods

All analyses will be performed on the treatment and follow-up phases.

All lab parameters with numeric values will be analyzed using descriptive statistics on actual values and changes from baseline over time.

Lab toxicity grade and abnormality will be described by frequency and percentage of subjects using below methods:

- Tabulation of the worst treatment-emergent toxicity grade of laboratory parameters
- Tabulation by worst grade of laboratory parameters where at least one subject had worst treatment emergent WHO toxicity grade >=3 during the Treatment Phase
- Cross-tabulation of the worst toxicity grades versus baseline
- Cross-tabulation of toxicity grades versus baseline over time
- Cross-tabulation of the worst laboratory parameter abnormalities versus baseline

Below plots and graphs will be produced to describe the overall and individual evaluations for selected laboratory parameters by timepoints:

- Plots of mean(SE) by treatment group over time (selected laboratory parameters*)
- Spaghetti plots of the selected laboratory parameters by treatment group based on actual values for the patients who had abnormality on treatment or follow-up phase

- Bar graphs of the treatment emergent abnormality by toxicity grade over time for selected laboratory parameters

Selected lab parameters* include ALT, AST, total bilirubin, indirect bilirubin, direct bilirubin, lipase, amylase, ALP, gamma-glutamyl transferase (GGT), creatine kinase, B-type natriuretic peptide (BNP) and estimated glomerular filtration rate (e-GFR).

Listings will be provided for all laboratory parameters, and the subjects who had grade 3 or greater laboratory results separately. The lab results for subjects who had cardiac events will be provided as well.

Pregnancy test results will be listed as well.

6.3. Vital Signs and Physical Examination Findings

Vital signs are assessed at following timepoints: Screening, Baseline, Weeks 2, 4, 6, 8 (for Arm B), EOT, FU Week 4, and Week 24.

Baseline is the day 1 measurement, if available. If not available the Screening value will be used.

The following vital signs parameters will be analyzed:

- Pulse/heart rate (bpm): supine
- Systolic blood pressure, SBP (mmHg): supine
- Diastolic blood pressure, DBP (mmHg): supine

6.3.1. Definitions

Pulse, DBP and SBP are classified in the following abnormality codes:

	Pulse (bpm)	**DBP (mmHg)**	**SBP (mmHg)**
Abnormally low	≤ 50	≤ 50	≤ 90
Grade 1 or mild	-	> 90 - < 100	> 140 - < 160
Grade 2 or moderate	-	≥ 100 - < 110	≥ 160 - < 180
Grade 3 or severe	-	≥ 110	≥ 180
Abnormally high	≥ 120	-	-

In determining the abnormalities, the following rules are applied:

- The worst grades/abnormalities are determined over the whole observational period (over both the treatment and follow-up phases), including post-baseline scheduled and unscheduled measurements
- The abnormalities ‘abnormally low’ and ‘abnormally high’/grades are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally

high or graded value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)

Treatment-emergent

An abnormality (abnormality based on the definition above) will be considered treatment-emergent if it is worse than the baseline. If the baseline is missing, the abnormality is always considered as treatment-emergent. A shift from 'abnormally low' at baseline to 'abnormally high' or 'grade …' post baseline (or vice versa) is also treatment-emergent.

6.3.2. Analysis Methods

All analyses will be performed on the treatment and follow-up phases.

Vital signs data will be analyzed using descriptive statistics on actual values and change from baseline over time.

Abnormality of vital signs will be described by frequency and percentage using below methods:

- Tabulation of the worst treatment-emergent abnormality of vital signs
- Tabulation of normality/abnormality of vital signs over time
- Cross-tabulations for the worst abnormality versus baseline

Plots of mean (SE) by treatment group over time will be provided for all vital signs parameters. A listing of abnormalities of vital signs (all parameters) will be provided as well.

Physical examination data will only be listed.

6.4. Electrocardiogram Parameters

The triplicate electrocardiogram (ECG) are available for the following time points: Screening, Baseline, D2, D3, Weeks 1-4, 6, 8 (for Arm B), and FU Week 4. Baseline is the Day 1 measurement, if available. If not available the Screening value will be used.

The mean of the triplicate ECGs will be analyzed. The ECG parameters include:

- Heart rate
- PR interval
- QRS interval
- RR interval

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- QT interval corrected for heart rate according to Bazett's QT formula (QTcB) (if available)
- QT interval corrected for heart rate according to Fridericia's QT formula (QTcF) (if available)

6.4.1. Definitions

For absolute HR, PR and QRS, the following abnormality categories are defined:

	HR	PR	QRS
abnormally low	≤ 50 bpm	< 120 ms	NAP
abnormally high	≥ 120 bpm	> 200 ms	≥ 120 ms

Per protocol, toxicity grading for PR interval will be performed according to the Division of Aids (DAIDS) grading table for the severity of adult and pediatric adverse events version 1.0, December 2004; clarification August 2009. Please see below:

Parameter	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially life-threatening**
Prolonged PR interval				
Adult >16 years	PR interval 0.20 – 0.25 sec*	PR interval >0.25 sec	Type II 2nd degree AV block OR Ventricular pause >3.0 sec	Complete AV block

*Revised by the sponsor.

The toxicity of PR interval will also be coded using the DAIDS grading table (version 2.0, dated 2014) as follows (http://rsc.tech-res.com/docs/default source/safety/daids_ae_grading_table_v2_nov2014.pdf?sfvrsn=8):

Grade 1: 210 to < 250 ms

Grade 2: ≥ 250 ms OR Type I 2nd degree AV block

Grade 3: Type II 2nd degree AV block OR Ventricular pause ≥ 3000 ms

Grade 4: Complete AV block

Analysis for PR will be conducted for all of definitions above (Abnormally high vs low, and toxicity grade per protocol and DAIDS 2.0).

Please note the information for ventricular pause will be provided from medical team.

For absolute QTc parameters the following abnormality categories are defined:

- QTc ≤ 450 ms (normal)
- 450 ms < QTc ≤ 480 ms (borderline)
- 480 ms < QTc ≤ 500 ms (prolonged)

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- QTc > 500 ms (pathologically prolonged)

For increases from baseline in QTc (ms) the following categories are defined:

- < 30 ms (normal)
- [30; 60] ms (borderline)
- > 60 ms (abnormally high)

Only increases in QTc ≥ 30 ms will be considered as abnormalities.

In determining the abnormalities, the following rules are applied:

- The worst abnormalities are determined over the whole observational period (over both the treatment and follow-up phases), including post-baseline scheduled and unscheduled measurements
- The abnormalities 'abnormally low' and 'abnormally high' are considered equally important, i.e. if a subject has as well an abnormally low as an abnormally high value post-baseline, both abnormalities are shown in the tables. (This means that the sum of the percentages can be more than 100%)

Treatment-emergent

An abnormality will be considered treatment-emergent if it is worse than the baseline. If the baseline is missing, the abnormality is always considered as treatment-emergent. A shift from 'abnormally low' at baseline to 'abnormally high' post baseline (or vice versa) is also treatment-emergent.

6.4.2. Analysis Methods

All analyses will be performed on the treatment and follow-up phases.

ECG parameters will be analyzed using descriptive statistics on actual values and change from baseline over time.

Overall ECG interpretations, such as Normal and Abnormal, which are collected in eCRF, will be summarized by timepoint. Also for individual ECG parameters, the abnormality will be tabulated using frequency and percentage through below methods:

- Tabulation of the worst treatment-emergent ECG abnormalities
- Tabulation of ECG normality/abnormalities over time
- Cross-Tabulation of the worst ECG abnormalities in actual value versus the baseline value
- Cross-Tabulation of the worst QTc increase versus the abnormality on the actual value

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Plots of actual mean(SE), mean of change from baseline(SE) by treatment group over time will be produced. Spaghetti plots of ECG parameters based on actual values and change from baseline will be produced for patients who had treatment-emergent abnormalities. Spaghetti plots of PR for the patients who had prolonged PR interval or AV block (grade>=1) will be produced too.

A listing of ECG abnormalities (all parameters) will be provided. It will contain both actual and change from baseline values.

6.5. Echocardiographic(ECHO) Parameters

ECHO data is available for the Screening, Week 4, and FU Week 4. The screening value will be used as the baseline.

ECHO parameters include:

- Left ventricular (LV) ejection fraction (EF) single plane (%)
- LV fractional shortening (%)
- LV posterior wall (LVPW) diastolic thickness (cm)
- Systolic volume (mL)
- Diastolic volume (mL)

6.5.1. Definitions

The following definitions are applicable to the ECHO analyses:

- Reversible decrease in LVEF is defined as a decrease of >10% from baseline, which is followed by an increase or a decrease of <=5% from baseline.

- No resolution in LVEF is defined as a decrease of >10% from baseline, which is NOT followed by an increase or a decrease of <=5% from baseline.

6.5.2. Analysis Methods

All analyses will be performed over the treatment and follow-up phases.

ECHO parameters will be analyzed using descriptive statistics on actual values, change from baseline and percentage change from baseline over time.

Number and percentage of subjects with abnormality based on normal ranges will be summarized over time for each ECHO parameter.

The maximum change from baseline in LVEF will be tabulated. It includes the number and percent of subjects with LVEF decline of > 10% from baseline or <=10% from baseline, decline of >= 10% and resulting in an LVEF < 50%, decrease in LVEF >10%

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from baseline with reversible decrease in LVEF or with no resolution, the summary of the time of onset and duration when LVEF decrease >10%, and LVEF increase > 10% etc.

Number and percentage of subjects will be summarized by visit for subjects who have a decrease in LVEF of:

- >5% but <=10%
- >10%

Below graphs will be produced:

- Plots of actual mean (SE), mean of change from baseline (SE) will be produced by treatment group over time
- Spaghetti plots based on actual values for each ECHO parameter by treatment group for the patients who had abnormal values during any post-dose time point (Week 4, and FU Week 4)

A listing of ECHO with actual value, change from baseline, % change from baseline for all parameters will be provided as well.

6.6. Graphical Patient Profiles

A set of graphical patient profiles will be produced for each subject. Data presented will include baseline characteristics, medical history, disposition, study drug exposure, HCVRNA levels, and concomitant medications.

7. PATIENT-REPORTED OUTCOMES (PRO)

This section contains statistical methods for the analysis of the PRO data. Further analysis may be conducted and reported separately to support psychometric validation of PRO instruments.

The following patient-reported outcomes (PRO) assessments will be evaluated:

- CLDQ-HCV (Chronic Liver Disease Quality of Life)
- EQ-5D-5L (Health Status and Quality of Life)
- FSS (Fatigue Severity Scale)
- SF-36v2 (Short Form-36 version 2)

The number (and percentage) of subjects completing each PRO instrument at each time points will be tabulated.

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7.1. CLDQ-HCV

7.1.1. Definitions

The CLDQ-HCV is a validated disease-specific instrument to assess health-related quality of life (HRQoL) in patients with chronic hepatitis C. The instrument covers HRQoL concepts including fatigue, activity, emotional function, abdominal symptoms, systemic symptoms and worry. The CLDQ-HCV is comprised of 29 items. The answers to each of the items are from 1-7 on a Likert scale, with higher values representing better HRQoL.

CLDQ-HCV includes four HRQoL domains and a summary score[2, 3]. The domain scores and summary score are calculated as the average of the non-missing items:

- activity and energy (AE): average of items 1, 3, 4, 5, 7, 18
- emotional (EM): average of items 6, 8, 9, 11, 16, 23, 24, 27, 28
- worry (WO): average of items 14, 15, 17, 19, 20, 21, 22, 29
- systemic (SY): average of items 2, 10, 12, 13, 25, 26
- CLDQ-HCV summary score: average of the 4 domain scores

A score will be derived if at least 50% of the items or domain scores are available respectively.

7.1.2. Analysis Methods

Descriptive statistics for the actual and change from baseline values at each time point will be displayed for each derived parameter. In addition, mean changes from baseline will be explored per subgroup as defined in section 2.4. The clinically important threshold of 0.5 will be used to interpret the mean change from baseline in the domain and summary scores.

The number (and percentage) of subjects with clinically important improvement/ worsening will be presented for each score. Clinically important thresholds are defined in section 7.5. The time (in weeks) to first clinically important improvement from baseline in CLDQ-HCV summary and domain scores during the treatment and follow-up phase will be graphically presented by means of Kaplan-Meier curves. If applicable, the median, 1st and 3rd quartiles of the time to first clinically important improvement from baseline will also be presented using point and interval estimates.

A cumulative distribution function will be drawn at different time points (baseline and changes from baseline at Week 4, EOT and the follow-up assessments).

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7.2. EQ-5D-5L

7.2.1. Definitions

The EQ-5D-5L evaluates a subject's self-rated health state on 5 dimensions. Additionally, a visual analogue scale (VAS) records the subject's self-rated health on a vertical, VAS.

The EQ-5D will be analyzed as follows:

- EQ-5D descriptive system: 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression); each with 5 response levels:
  - Level 1: indicating no problem
  - Level 2: indicating slight problems
  - Level 3: indicating moderate problems
  - Level 4: indicating severe problems
  - Level 5: indicating extreme problem

- EQ-5D VAS: a continuous score ranging from 0 to 100 (best imaginable health state=100 and worst imaginable health state=0)

- EQ-5D Valuation index (VI): The information of the 5 dimensions of the descriptive system summarized into one index (a weighted scoring of the 5 dimension scores with a possible range from 0 to 1)

  a. Assign the level code 1 to 5 to each level of the 5 dimensions

  b. Create a health state for each patient-time point combination. A health state is a combination of 5 level codes; one level code for each dimension. The dimensions are ordered as described above.
  E.g. health state 12311 indicates 'no problems in walking about, slight problems washing or dressing myself, moderate problems doing usual activities, no pain or discomfort, not anxious or depressed'.

  c. Assign an index value (valuation index) to each observed health state using the US crosswalk value set as defined in appendix 4. Based on the origin of the subjects, another method can be used.

Missing data

1) If – for a subject and time point – one (or more) dimensions of the descriptive system are missing then
   - The EQ-5D VAS will be tabulated if non-missing
   - The valuation index will not be tabulated
   - The non-missing dimensions of EQ-5D descriptive system will be summarized
2) If – for a subject and time point – the EQ-5D VAS is missing then the EQ-5D descriptive system and valuation index will be tabulated if complete.

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7.2.2. Analysis Methods

For the EQ-5D descriptive system, the number (and percentage) of subjects per dimension and problem level by time point will be tabulated. A shift table of the responses versus baseline will also be provided per dimension and time point.

For the EQ-5D VAS and for the Valuation index, descriptive statistics for the actual and change from baseline values at each time point will be displayed. In addition, mean changes from baseline will be explored per subgroup as defined in section 2.4. The clinically important threshold of 8 will be used to interpret the mean change from baseline in the VAS.

To assess the effect of treatment on EQ-5D VAS, within-treatment comparisons will be performed in a cross-sectional manner per time points using Wilcoxon signed-rank test (paired test with subject's own baseline). To assess the impact of treatment duration on VAS, a between-group comparison of the changes from baseline will be performed at EOT, FU Week 4, FU Week 12 and FU Week 24 using Van Elteren test stratified by Prior HCV treatment history (Naive, Experienced) and HCV geno/subtype (genotypes 1a or 2 versus genotypes 1b, 4, 5 or 6). The tests will be conducted at a significance level of 0.05, 2-sided.

The number (and percentage) of subjects with clinically important improvement/ worsening will be presented for EQ-5D VAS. The time (in weeks) to first clinically important improvement from baseline in EQ-5D VAS during the treatment and follow-up phase will be graphically presented by means of Kaplan-Meier curves. If applicable, the median, 1st and 3rd quartiles of the time to first clinically important improvement from baseline will also be presented using point and interval estimates.

A cumulative distribution function of the EQ-5D VAS will be drawn at different time points (baseline and changes from baseline at Week 4, EOT and the follow-up assessments).

7.3. FSS

7.3.1. Definitions

The Fatigue Severity Scale (FSS) is an instrument with 9 items. Item responses are measured on a 7-point Likert scale ranging from strongly disagree (1 point) to strongly agree (7 points). Higher response values indicate higher level of fatigue.

The 9 items are combined into one total score. If the number of missing items is less than 4, the total score is the average of the non-missing items; else the total score is missing.

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7.3.2. Analysis Methods

Descriptive statistics for the actual and change from baseline values at each time point will be displayed. In addition, mean changes from baseline in the FSS will be explored per subgroup as defined in section 2.4. The clinically important threshold of 0.5 will be used to interpret the mean change from baseline in the total FSS score.

To assess the effect of treatment on FSS, within-treatment comparisons will be performed in a cross-sectional manner per time points using Wilcoxon signed-rank test (paired test with subject's own baseline). To assess the impact of treatment duration on FSS, a between-group comparison of the changes from baseline will also be performed at EOT, FU Week 4, FU Week 12 and FU Week 24 using Van Elteren test stratified by Prior HCV treatment history (Naive, Experienced) and HCV geno/subtype (genotypes 1a or 2 versus genotypes 1b, 4, 5 or 6). The tests will be conducted at a significance level of 0.05, 2-sided.

The number (and percentage) of subjects with clinically important improvement/ worsening will be presented for FSS. The time (in weeks) to first clinically important improvement from baseline in FSS during the treatment and follow-up phase will be graphically presented by means of Kaplan-Meier curves. If applicable, the median, 1st and 3rd quartiles of the time to first clinically important improvement from baseline will also be presented using point and interval estimates.

A cumulative distribution function will be drawn at different time points (baseline and changes from baseline at Week 4, Week 8, EOT and the follow-up assessments).

7.4. SF-36v2

7.4.1. Definitions

SF-36v2 is a generic 36-item instrument measuring HRQoL, where participants self-report on items in a domain scale that have between 2-6 response choices per item using Likert-type responses (eg, none of the time, some of the time, etc.). SF-36v2 can be interpreted using T-scores from 8 domain scales and 2 summary scores – Physical Component Summary (PCS) and Mental Component Summary (MCS).

Responses to all items will be used to derive the 8 health domain scales except item #2. No recoding will be done for item #2; the original response will be tabulated. Each of the 8 domain scales will be derived by first taking the sum of the responses per domain[1]:

- Physical Functioning (PF): 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j
- Role-Physical (RP): 4a, 4b, 4c, 4d
- Bodily Pain (BP): 7, 8
- General Health (GH): 1, 11a, 11b, 11c, 11d
- Vitality (VT): 9a, 9e, 9g, 9i

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- Social Functioning (SF): 6, 10
- Role-Emotional (RE): 5a, 5b, 5c
- Mental Health (MH): 9b, 9c, 9d, 9f, 9h

The total domain scores of domain scales will be transformed into a range from 0 to 100; 0=worst HRQoL, 100=best HRQoL. The scores (0-100 scores) will then be standardized using means and standard deviations from the 2009 U.S. general population, and converted to norm-based scores using a T-score transformation (mean = 50, SD = 10) [1]. Two aggregate component scores will be derived as linear combination of the standardized (2009 U.S. norm) scores using weights from principal component analysis. Each aggregate component score will be transformed to the corresponding PCS T-score and MCS T-score (mean = 50, SD = 10) [1].

The domain scale scores and component summary scores will be calculated using the QualityMetric Health Outcomes™ Scoring Software, version 4.5.1 or a later version. In case of missingness the Full Missing Score Estimation (MSE) method or Item Response Theory (IRT) will be used, if applicable, for imputation of missing values[1]. SF-36v2 item #2, the health domain scale T-scores, PCS T-scores and MCS T-scores will be analyzed.

7.4.2. Analysis Methods

Descriptive statistics for the actual and change from baseline at each time point will be displayed. In addition, mean changes from baseline in health domain scale and summary measures will be explored per subgroup as defined in section 2.4. Clinically important threshold (5 for subscales and 5 for summary measures) will be used to interpret the mean change from baseline. Frequency tabulation (n, %) of the response categories of item #2 of the SF-36v2 instrument will be tabulated per time point for each treatment group.

The number (and percentage) of subjects with clinically important improvement/ worsening will be presented. The time (in weeks) to first clinically important improvement from baseline in PCS and MCS during the treatment and follow-up phase will be graphically presented by means of Kaplan-Meier curves. If applicable, the median, 1st and 3rd quartiles of the time to first clinically important improvement from baseline will also be presented using point and interval estimates.

A cumulative distribution function will be drawn at different time points (baseline and changes from baseline at Week 4, Week 8, EOT and the follow-up assessments).

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7.5. Proposed Thresholds Indicating Clinically Important Changes from Baseline in PRO

PRO Instrument	Mean Change[a] from baseline	Individual Subject's Change[a] from baseline
CLDQ-HCV		
4 domain scores	≥0.5 point	≥0.5 point
summary score	≥0.5 point	≥0.5 point
EQ-5D VAS score	≥8 points	≥8 points
FSS Total score	≥0.5 point	≥1 point
SF-36v2		
PCS	≥5 points	≥5 points
MCS	≥5 points	≥5 points
8 domain scores	≥5 points	≥5 points

[a] This change refers to either an increase or a decrease >= threshold

8. PHARMACOKINETICS/PHARMACODYNAMICS

8.1. Pharmacokinetics

Blood samples for PK assessments of AL-335 (and its 2 metabolites ALS-399 and ALS-227), ODV, and SMV will be collected from all subjects at the Week 4 visit, the Week 6 visit (arm B) and at the EOT visit at any time during the visit.

Based on the individual plasma concentration-time data from all subjects, exposure parameters of AL-335 (and its two metabolites), ODV, and SMV will be derived using population PK (popPK) modelling. The following exposure parameters for AL-335 (and metabolites), ODV, and SMV will be derived using nonlinear mixed-effects modelling: AUC_{24h}, C_{0h}, and C_{max} (if popPK model allows the estimation of C_{max}).

These exposure parameters will be derived at the Week 4 visit and at the EOT visit (week 6 arm A), and at the Week 4 visit, Week 6 visit and at the EOT visit (week 8 arm B). The mean value over these visits for each exposure parameter of AL-335, ALS-399, ALS-227, ODV and SMV will be used in tabulations and plots described in section 9.1.1.

8.1.1. Analysis methods

Descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, maximum, and geometric mean will be presented for each exposure parameter (AUC_{24h}, C_{0h}, and C_{max} if model allows) of AL-335 (and metabolites), ODV, and SMV for each treatment group and also pooled over treatment groups.

Box and whisker plots for each exposure parameter (AUC_{24h}, C_{0h}, and C_{max}) of AL-335 (and metabolites), ODV, and SMV will be presented by treatment group and also pooled over treatment groups.

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8.2. Pharmacokinetic/ Pharmacodynamic Analyses

Each exposure parameter (AUC_{24h}, C_{0h}, and C_{max}if model allows) of AL-335 (and metabolites), ODV, and SMV will be categorized into quartiles for each treatment group.
Relationships of AL-335 (and metabolites), ODV, and SMV population-derived exposure parameters (AUC_{24h}, C_{0h}, and C_{max}) with efficacy will be explored as follows.
The number and percentage of subjects with the following by quartiles of the exposure parameters of AL-335 (and metabolites), ODV, and SMV will be tabulated for each treatment group:

- SVR12
- RVR
- SVR4
- SVR24
- On-treatment failure (also broken down by type of failure: Viral breakthrough; Confirmed HCV RNA ≥ LLOQ at EOT; Other)
- Not detected at EOT
- Viral relapse

Box and whisker plots for each exposure parameter (AUC_{24h}, C_{0h}, and C_{max}) of AL-335 (and metabolites), ODV, and SMV for each treatment group will be presented by each efficacy response.
For each treatment group the following scatterplots will be produced:

- ODV AUC_{24h} versus SMV AUC_{24h}.
- ODV AUC_{24h} versus ALS-227 AUC_{24h}
- SMV AUC_{24h} versus ALS-227 AUC_{24h}

Different colors will be used to distinguish between subjects achieving SVR12 and those not achieving SVR12.
For each of AL-335 (and metabolites), ODV, and SMV, a scatterplot of change in HCV RNA from baseline to Day 7 versus AUC_{24h} and a scatterplot of the actual HCV RNA value at Week 4 versus AUC_{24h} will be presented.
Relationships of AL-335 (and metabolites), ODV, and SMV population-derived exposure parameters (AUC_{24h}, and C_{max}) with safety will be explored as follows.
The number and percentage of subjects with the following by quartiles of the exposure parameters of AL-335 (and metabolites), ODV, and SMV will be tabulated for each treatment group:

- Any AE
- Any AE worst grade 1 or 2
- Any AE worst grade 3 or 4
- Any AE at least possibly related to AL-335+ODV+SMV (any drug)
- Any AE with fatal outcome
- Any SAE
- Any SAE at least possibly related to AL-335+ODV+SMV (any drug)
- AE leading to permanent stop of All Study Medication
- AE leading to temporary interruption of All Study Medication

The number and percentage of subjects with the following by quartiles of the exposure parameters of AL-335 will be tabulated for each treatment group:

- Any AE at least possibly related to AL-335
- Any SAE at least possibly related to AL-335
- AE leading to permanent stop of AL-335
- AE leading to temporary interruption of AL-335

The number and percentage of subjects with the following by quartiles of the exposure parameters of ODV will be tabulated for each treatment group:

- Any AE at least possibly related to ODV
- Any SAE at least possibly related to ODV
- AE leading to permanent stop of ODV
- AE leading to temporary interruption of ODV

The number and percentage of subjects with the following by quartiles of the exposure parameters of SMV will be tabulated for each treatment group:

- Any AE at least possibly related to SMV
- Any SAE at least possibly related to SMV
- AE leading to permanent stop of SMV
- AE leading to temporary interruption of SMV

Only treatment emergent adverse events will be tabulated.
The number and percentage of subjects with the following adverse events of interest by quartiles of the exposure parameters of AL-335 (and metabolites), ODV, and SMV will be tabulated for each treatment group.

- Cardiac events
- Increased Bilirubin
- Rash (all types)

Box and whisker plots for each exposure parameter of AL-335 (and metabolites), ODV, and SMV for each treatment group will be presented by for subjects with and without each type of event of interest given above.
The number and percentage of subjects with treatment-emergent PR abnormally high (PR > 200 ms) and the number and percentage of subjects in each PR interval category during the treatment phase will be tabulated by exposure quartile of AL-335 (and metabolites), ODV, and SMV for each parameter and treatment group. The worst PR value during the treatment phase will be used to determine abnormality and PR interval category (<120 ms, >=120 - <=200 ms, >200 - <=240 ms, >240 - <=300 ms, >300 ms).
Box and whisker plots for each exposure parameter of AL-335 (and metabolites), ODV, and SMV for each treatment group will be presented by for subjects with and without treatment emergent PR abnormally high.
The maximum change from baseline in selected laboratory parameters (ALT, AST, CK, total bilirubin, direct bilirubin, indirect bilirubin, and BNP) during the treatment phase will be plotted versus AUC_{24h} for each of AL-335 (and metabolites), ODV, and SMV.

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9. HEALTH ECONOMICS

Medical resource utilization will be summarized descriptively.

Occupational/employment status will also be descriptively summarized by treatment arm.

10. REFERENCES

1. Maruish, M. E. (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated
2. Younossi, Z. M., Boparai, N., McCormick, M. (2000) A disease-specific health-related quality of life instrument for chronic hepatitis C: CLDQ-HCV. *Hepatology. 32*, 838.
3. Younossi, Z. M., Stepanova, M., Henry L. (2016). Performance and validation of chronic liver disease questionnaire-hepatitis C version (CLDQ-HCV) in clinical trials of patients with chronic hepatitis C. *Elsevier, 19*, 544–551.

APPENDIX 1: PHASE ALLOCATION/COMBINING AES

STEP 1: allocation of events to the phases

Adverse events present in the SDS database are allocated to phases based on their start date. If the start date of an event falls between (or on) the start and stop date of a phase, the AE is attributed to that phase.

Incomplete dates (i.e. *day and/or month and/or year missing*)

- Partial start or stop dates:

    1. The partial start date (i.e. missing day) will be imputed with the first day of the month unless the month/year is the same as the month/year of an analysis phase. In this situation the incomplete start date will be imputed with the start date of that phase. If the start date of the year is given without specification of the month and date, the partial missing start date will be imputed with the maximum of the first day of the given year and the first date of the first phase.

    2. The partial missing end date (i.e. missing day) will be imputed with the last day of the month. If the end date of the year is given without specification of the month and date, the partial missing end date will be imputed with the minimum of the last day of the given year and the end date of the last phase.

- Completely missing start date: the event is allocated to the first active treatment phase (the start date is imputed with the treatment phase start date), except if the end date of the AE falls before the start of the first active treatment phase, in which case it is assigned to the screening phase (the start date is imputed with the screening phase start date).

- Completely missing end date: the following decision rules apply

    1) For completed and discontinued subjects:

        - In case the end date is not flagged as ongoing the date will remain missing.
        - In case the end date is flagged as ongoing the date is imputed by the end date of the last phase.

    2) For ongoing subjects:

        - Missing end dates are imputed by the end date of the last phase (i.e. the cut-off date).

STEP 2: combining adverse events

Overlapping/consecutive events are defined as events of the same subject with the same preferred term who have at least 1 day in overlap or for which the start date of an event is 1 day after the end date of the preceding event. Overlapping/consecutive events may be combined into one AE or not, according to the following rules:

1) In case a non-active phase (e.g. Screening) is followed by an active phase, and the overlapping/consecutive events start in both phases, they are allocated to their respective phase and are considered as separate events.

2) In case overlapping/consecutive events start within a single phase, they are considered as one and the same AE. The individual events who contribute to this AE are retained as individual records in the ADAM database but are assigned the same onset, phase, and total duration.

3) In case an active phase is followed by a non-active phase (e.g. Follow-Up), and the overlapping/consecutive events start in both phases, they are allocated to the active phase and are considered as one and the same AE. The individual events who contribute to this AE are retained as individual records in the ADAM database but are assigned the same duration, onset and active phase.

4) In case a non-active phase is followed by a non-active phase, and the overlapping/consecutive events start in both phases, they are allocated to their respective phase and are considered as separate AEs.

Events can only be combined into one and the same AE if their start and stop dates are complete. In case the completely missing end date is imputed, this date is also considered as a complete date.

APPENDIX 2A: SEARCH TERMS FOR EVENTS OF SPECIAL/CLINICAL INTEREST

	MedrDRA Term Level	Searching Terms
Events of special interest		
Cardiac Events	SMQ	Please see Appendix 3
Increased Bilirubin	MedDRA PTs	Bilirubin conjugated abnormal Bilirubin conjugated increased Bilirubin excretion disorder Bilirubinuria Blood bilirubin abnormal Blood bilirubin increased

		Blood bilirubin unconjugated increased Hyperbilirubinaemia Icterus index increased Jaundice Jaundice cholestatic Jaundice extrahepatic obstructive Jaundice hepatocellular Ocular icterus Urine bilirubin increased Yellow skin
Events of clinical interest		
Rash (all type)	MedDRA HLTs, PTs	Erythemas - HLT Papulosquamous conditions - HLT Rashes, eruptions and exanthems NEC - HLT PT: Photodermatosis Photosensitivity reaction Polymorphic light eruption Solar dermatitis Sunburn
	SMQ	SMQ-Severe cutaneous adverse reaction: narrow scope and selected terms of the broad scope(refer APPENDIX 3)
Pruritus	MedDRA HLT	Pruritus NEC
Photosensitivity conditions	MedDRA PTs	Photodermatosis Photosensitivity reaction Polymorphic light eruption Solar dermatitis Sunburn

APPENDIX 2B: RASH – SMQ19.1

SMQ 19.1: “Severe cutaneous adverse reaction”

SCOPE	Preferred Term
NARROW	CUTANEOUS VASCULITIS
NARROW	DERMATITIS BULLOUS
NARROW	DERMATITIS EXFOLIATIVE
NARROW	DERMATITIS EXFOLIATIVE GENERALISED
NARROW	ERYTHEMA MULTIFORME
NARROW	OCULOMUCOCUTANEOUS SYNDROME
NARROW	SKIN NECROSIS
NARROW	STEVENS-JOHNSON SYNDROME
NARROW	TOXIC EPIDERMAL NECROLYSIS
NARROW	ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS

NARROW	TOXIC SKIN ERUPTION
NARROW	EPIDERMAL NECROSIS
NARROW	EXFOLIATIVE RASH
NARROW	DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS
BROAD	BLISTER
BROAD	BULLOUS IMPETIGO
BROAD	DRUG ERUPTION
BROAD	EPIDERMOLYSIS BULLOSA
BROAD	MUCOCUTANEOUS ULCERATION
BROAD	NIKOLSKY'S SIGN
BROAD	PEMPHIGOID
BROAD	PEMPHIGUS
BROAD	SKIN EROSION
BROAD	SKIN EXFOLIATION
BROAD	EPIDERMOLYSIS
BROAD	ACQUIRED EPIDERMOLYSIS BULLOSA

APPENDIX 3: CARDIAC EVENTS - SMQ19.1

				Narrow/Broad	PT Term
Cardiac arrhythmias (SMQ)					
	Arrhythmia related investigations, signs and symptoms (SMQ)				
				Narrow	Chronotropic incompetence
				Narrow	Electrocardiogram repolarisation abnormality
				Narrow	Electrocardiogram RR interval prolonged
				Narrow	Electrocardiogram U-wave abnormality
				Narrow	Sudden cardiac death
				Broad	Bezold-Jarisch reflex
				Broad	Bradycardia
				Broad	Cardiac arrest
				Broad	Cardiac death
				Broad	Cardiac telemetry abnormal
				Broad	Cardio-respiratory arrest
				Broad	Central bradycardia
				Broad	Electrocardiogram abnormal
				Broad	Electrocardiogram ambulatory abnormal
				Broad	Electrocardiogram change
				Broad	Heart rate abnormal
				Broad	Heart rate decreased

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				Broad	Heart rate increased
				Broad	Loss of consciousness
				Broad	Palpitations
				Broad	Rebound tachycardia
				Broad	Sudden death
				Broad	Syncope
				Broad	Tachycardia
				Broad	Tachycardia paroxysmal
	Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ)				
		Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)			
			Bradyarrhythmia terms, nonspecific (SMQ)		
				Narrow	Bradyarrhythmia
				Narrow	Ventricular asystole
			Conduction defects (SMQ)		
				Narrow	Accessory cardiac pathway
				Narrow	Adams-Stokes syndrome
				Narrow	Agonal rhythm
				Narrow	Atrial conduction time prolongation
				Narrow	Atrioventricular block
				Narrow	Atrioventricular block complete
				Narrow	Atrioventricular block first degree
				Narrow	Atrioventricular block second degree
				Narrow	Atrioventricular conduction time shortened
				Narrow	Atrioventricular dissociation
				Narrow	Bifascicular block
				Narrow	Brugada syndrome
				Narrow	Bundle branch block
				Narrow	Bundle branch block bilateral
				Narrow	Bundle branch block left
				Narrow	Bundle branch block right
				Narrow	Conduction disorder
				Narrow	Defect conduction intraventricular
				Narrow	Electrocardiogram delta waves abnormal
				Narrow	Electrocardiogram PQ interval prolonged
				Narrow	Electrocardiogram PQ interval shortened
				Narrow	Electrocardiogram PR prolongation
				Narrow	Electrocardiogram PR shortened
				Narrow	Electrocardiogram QRS complex prolonged
				Narrow	Electrocardiogram QT prolonged
				Narrow	Electrocardiogram repolarisation abnormality

				Narrow	Lenegre's disease
				Narrow	Long QT syndrome
				Narrow	Paroxysmal atrioventricular block
				Narrow	Sinoatrial block
				Narrow	Trifascicular block
				Narrow	Ventricular dyssynchrony
				Narrow	Wolff-Parkinson-White syndrome
			Disorders of sinus node function (SMQ)		
				Narrow	Nodal arrhythmia
				Narrow	Nodal rhythm
				Narrow	Sinus arrest
				Narrow	Sinus arrhythmia
				Narrow	Sinus bradycardia
				Narrow	Sinus node dysfunction
				Narrow	Wandering pacemaker
		Cardiac arrhythmia terms, nonspecific (SMQ)			
				Narrow	Arrhythmia
				Narrow	Heart alternation
				Narrow	Heart rate irregular
				Narrow	Pacemaker generated arrhythmia
				Narrow	Pacemaker syndrome
				Narrow	Paroxysmal arrhythmia
				Narrow	Pulseless electrical activity
				Narrow	Reperfusion arrhythmia
				Narrow	Withdrawal arrhythmia
		Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ)			
			Supraventricular tachyarrhythmias (SMQ)		
				Narrow	Arrhythmia supraventricular
				Narrow	Atrial fibrillation
				Narrow	Atrial flutter
				Narrow	Atrial parasystole
				Narrow	Atrial tachycardia
				Narrow	Junctional ectopic tachycardia
				Narrow	Sinus tachycardia
				Narrow	Supraventricular extrasystoles
				Narrow	Supraventricular tachyarrhythmia
				Narrow	Supraventricular tachycardia
				Broad	ECG P wave inverted
				Broad	Electrocardiogram P wave abnormal
				Broad	Retrograde p-waves
			Tachyarrhythmia terms, nonspecific (SMQ)		
				Narrow	Anomalous atrioventricular excitation
				Narrow	Cardiac fibrillation
				Narrow	Cardiac flutter

				Narrow	Extrasystoles
				Narrow	Tachyarrhythmia
			Ventricular tachyarrhythmias (SMQ)		
				Narrow	Accelerated idioventricular rhythm
				Narrow	Cardiac fibrillation
				Narrow	Parasystole
				Narrow	Rhythm idioventricular
				Narrow	Torsade de pointes
				Narrow	Ventricular arrhythmia
				Narrow	Ventricular extrasystoles
				Narrow	Ventricular fibrillation
				Narrow	Ventricular flutter
				Narrow	Ventricular parasystole
				Narrow	Ventricular pre-excitation
				Narrow	Ventricular tachyarrhythmia
				Narrow	Ventricular tachycardia
Cardiac failure (SMQ)					
				Narrow	Acute left ventricular failure
				Narrow	Acute pulmonary oedema
				Narrow	Acute right ventricular failure
				Narrow	Cardiac asthma
				Narrow	Cardiac failure
				Narrow	Cardiac failure acute
				Narrow	Cardiac failure chronic
				Narrow	Cardiac failure congestive
				Narrow	Cardiac failure high output
				Narrow	Cardiogenic shock
				Narrow	Cardiopulmonary failure
				Narrow	Cardiorenal syndrome
				Narrow	Chronic left ventricular failure
				Narrow	Chronic right ventricular failure
				Narrow	Cor pulmonale
				Narrow	Cor pulmonale acute
				Narrow	Cor pulmonale chronic
				Narrow	Ejection fraction decreased
				Narrow	Hepatic congestion
				Narrow	Hepatojugular reflux
				Narrow	Left ventricular failure
				Narrow	Low cardiac output syndrome
				Narrow	Neonatal cardiac failure
				Narrow	Obstructive shock
				Narrow	Pulmonary oedema
				Narrow	Pulmonary oedema neonatal
				Narrow	Radiation associated cardiac failure

				Narrow	Right ventricular ejection fraction decreased
				Narrow	Right ventricular failure
				Narrow	Ventricular failure
				Broad	Artificial heart implant
				Broad	Atrial natriuretic peptide abnormal
				Broad	Atrial natriuretic peptide increased
				Broad	Bendopnoea
				Broad	Brain natriuretic peptide abnormal
				Broad	Brain natriuretic peptide increased
				Broad	Cardiac cirrhosis
				Broad	Cardiac contractility modulation therapy
				Broad	Cardiac index decreased
				Broad	Cardiac output decreased
				Broad	Cardiac resynchronisation therapy
				Broad	Cardiac ventriculogram abnormal
				Broad	Cardiac ventriculogram left abnormal
				Broad	Cardiac ventriculogram right abnormal
				Broad	Cardiomegaly
				Broad	Cardio-respiratory distress
				Broad	Cardiothoracic ratio increased
				Broad	Central venous pressure increased
				Broad	Diastolic dysfunction
				Broad	Dilatation ventricular
				Broad	Dyspnoea paroxysmal nocturnal
				Broad	Heart transplant
				Broad	Hepatic vein dilatation
				Broad	Jugular vein distension
				Broad	Left ventricular dilatation
				Broad	Left ventricular dysfunction
				Broad	Left ventricular enlargement
				Broad	Lower respiratory tract congestion
				Broad	Myocardial depression
				Broad	Nocturnal dyspnoea
				Broad	N-terminal prohormone brain natriuretic peptide abnormal
				Broad	N-terminal prohormone brain natriuretic peptide increased
				Broad	Oedema
				Broad	Oedema due to cardiac disease
				Broad	Oedema neonatal
				Broad	Oedema peripheral
				Broad	Orthopnoea
				Broad	Peripheral oedema neonatal
				Broad	Peripheral swelling

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				Broad	Post cardiac arrest syndrome
				Broad	Prohormone brain natriuretic peptide abnormal
				Broad	Prohormone brain natriuretic peptide increased
				Broad	Pulmonary congestion
				Broad	Right ventricular dilatation
				Broad	Right ventricular dysfunction
				Broad	Right ventricular enlargement
				Broad	Scan myocardial perfusion abnormal
				Broad	Stroke volume decreased
				Broad	Surgical ventricular restoration
				Broad	Systolic dysfunction
				Broad	Venous pressure increased
				Broad	Venous pressure jugular abnormal
				Broad	Venous pressure jugular increased
				Broad	Ventricular assist device insertion
				Broad	Ventricular dysfunction
				Broad	Ventricular dyssynchrony
Cardiomyopathy (SMQ)					
				Narrow	Atrial septal defect acquired
				Narrow	Biopsy heart abnormal
				Narrow	Cardiac amyloidosis
				Narrow	Cardiac hypertrophy
				Narrow	Cardiac sarcoidosis
				Narrow	Cardiac septal hypertrophy
				Narrow	Cardiac siderosis
				Narrow	Cardiomyopathy
				Narrow	Cardiomyopathy acute
				Narrow	Cardiomyopathy alcoholic
				Narrow	Cardiomyopathy neonatal
				Narrow	Cardiotoxicity
				Narrow	Congestive cardiomyopathy
				Narrow	Cytotoxic cardiomyopathy
				Narrow	Diabetic cardiomyopathy
				Narrow	Ejection fraction abnormal
				Narrow	Ejection fraction decreased
				Narrow	Eosinophilic myocarditis
				Narrow	HIV cardiomyopathy
				Narrow	Hypertensive cardiomyopathy
				Narrow	Hypertrophic cardiomyopathy
				Narrow	Ischaemic cardiomyopathy
				Narrow	Metabolic cardiomyopathy
				Narrow	Myocardial calcification
				Narrow	Myocardial fibrosis

				Narrow	Myocardial haemorrhage
				Narrow	Non-obstructive cardiomyopathy
				Narrow	Peripartum cardiomyopathy
				Narrow	Pulmonary arterial wedge pressure increased
				Narrow	Restrictive cardiomyopathy
				Narrow	Right ventricular ejection fraction decreased
				Narrow	Stress cardiomyopathy
				Narrow	Tachycardia induced cardiomyopathy
				Narrow	Thyrotoxic cardiomyopathy
				Narrow	Ventricular septal defect acquired
				Narrow	Viral cardiomyopathy
				Broad	Abnormal precordial movement
				Broad	Acquired cardiac septal defect
				Broad	Acute left ventricular failure
				Broad	Alcohol septal ablation
				Broad	Allergic myocarditis
				Broad	Arrhythmia
				Broad	Arrhythmia supraventricular
				Broad	Artificial heart implant
				Broad	Ascites
				Broad	Atrial hypertrophy
				Broad	Atrial pressure increased
				Broad	Autoimmune myocarditis
				Broad	Bendopnoea
				Broad	Blood pressure diastolic abnormal
				Broad	Blood pressure diastolic decreased
				Broad	Blood pressure diastolic increased
				Broad	Blood pressure fluctuation
				Broad	Blood pressure inadequately controlled
				Broad	Blood pressure systolic abnormal
				Broad	Blood pressure systolic decreased
				Broad	Blood pressure systolic increased
				Broad	Cardiac aneurysm
				Broad	Cardiac arrest
				Broad	Cardiac contractility modulation therapy
				Broad	Cardiac electrophysiologic study abnormal
				Broad	Cardiac failure
				Broad	Cardiac failure acute
				Broad	Cardiac failure chronic
				Broad	Cardiac failure congestive
				Broad	Cardiac function test abnormal
				Broad	Cardiac imaging procedure abnormal

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				Broad	Cardiac index abnormal
				Broad	Cardiac index decreased
				Broad	Cardiac index increased
				Broad	Cardiac monitoring abnormal
				Broad	Cardiac operation
				Broad	Cardiac output decreased
				Broad	Cardiac pseudoaneurysm
				Broad	Cardiac resynchronisation therapy
				Broad	Cardiac ventricular scarring
				Broad	Cardiac ventriculogram abnormal
				Broad	Cardiac ventriculogram left abnormal
				Broad	Cardiac ventriculogram right abnormal
				Broad	Cardiomegaly
				Broad	Cardiothoracic ratio increased
				Broad	Cardiovascular disorder
				Broad	Cardiovascular function test abnormal
				Broad	Chest pain
				Broad	Chest X-ray abnormal
				Broad	Computerised tomogram thorax abnormal
				Broad	Coxsackie carditis
				Broad	Coxsackie myocarditis
				Broad	Cytomegalovirus myocarditis
				Broad	Decreased ventricular preload
				Broad	Diastolic dysfunction
				Broad	Dilatation atrial
				Broad	Dilatation ventricular
				Broad	Directional Doppler flow tests abnormal
				Broad	Dyspnoea
				Broad	ECG signs of ventricular hypertrophy
				Broad	Echocardiogram abnormal
				Broad	Electrocardiogram abnormal
				Broad	Electrocardiogram change
				Broad	Endocardial fibroelastosis
				Broad	External counterpulsation
				Broad	Gonococcal heart disease
				Broad	Heart and lung transplant
				Broad	Heart transplant
				Broad	Hepatomegaly
				Broad	Hyperdynamic left ventricle
				Broad	Increased ventricular preload
				Broad	Irregular breathing
				Broad	Labile blood pressure
				Broad	Left atrial dilatation
				Broad	Left atrial enlargement

				Broad	Left ventricular dilatation
				Broad	Left ventricular end-diastolic pressure decreased
				Broad	Left ventricular enlargement
				Broad	Left ventricular failure
				Broad	Left ventricular heave
				Broad	Lupus myocarditis
				Broad	Lyme carditis
				Broad	Malarial myocarditis
				Broad	Mental status changes
				Broad	Multiple gated acquisition scan abnormal
				Broad	Myocardiac abscess
				Broad	Myocardial necrosis marker increased
				Broad	Myocarditis
				Broad	Myocarditis bacterial
				Broad	Myocarditis helminthic
				Broad	Myocarditis infectious
				Broad	Myocarditis meningococcal
				Broad	Myocarditis mycotic
				Broad	Myocarditis post infection
				Broad	Myocarditis septic
				Broad	Myocarditis syphilitic
				Broad	Myocarditis toxoplasmal
				Broad	Myoglobinaemia
				Broad	Myoglobinuria
				Broad	Nocturia
				Broad	Nuclear magnetic resonance imaging thoracic abnormal
				Broad	Oedema
				Broad	Orthostatic hypotension
				Broad	Palpitations
				Broad	Papillary muscle disorder
				Broad	Papillary muscle haemorrhage
				Broad	Radiation myocarditis
				Broad	Right atrial dilatation
				Broad	Right atrial enlargement
				Broad	Right atrial pressure increased
				Broad	Right ventricle outflow tract obstruction
				Broad	Right ventricular dilatation
				Broad	Right ventricular enlargement
				Broad	Right ventricular heave
				Broad	Right ventricular systolic pressure decreased
				Broad	Scan myocardial perfusion abnormal
				Broad	Sudden cardiac death

				Broad	Sudden death
				Broad	Surgical ventricular restoration
				Broad	Syncope
				Broad	Systolic anterior motion of mitral valve
				Broad	Systolic dysfunction
				Broad	Ultrasound Doppler abnormal
				Broad	Vascular resistance pulmonary increased
				Broad	Ventricular arrhythmia
				Broad	Ventricular assist device insertion
				Broad	Ventricular dysfunction
				Broad	Ventricular dyskinesia
				Broad	Ventricular dyssynchrony
				Broad	Ventricular hyperkinesia
				Broad	Ventricular hypertrophy
				Broad	Ventricular hypokinesia
				Broad	Ventricular remodelling
				Broad	Viral myocarditis
Ischaemic heart disease (SMQ)					
	Myocardial infarction (SMQ)				
				Narrow	Acute coronary syndrome
				Narrow	Acute myocardial infarction
				Narrow	Angina unstable
				Narrow	Blood creatine phosphokinase MB abnormal
				Narrow	Blood creatine phosphokinase MB increased
				Narrow	Coronary artery embolism
				Narrow	Coronary artery occlusion
				Narrow	Coronary artery reocclusion
				Narrow	Coronary artery thrombosis
				Narrow	Coronary bypass thrombosis
				Narrow	Coronary vascular graft occlusion
				Narrow	Kounis syndrome
				Narrow	Myocardial infarction
				Narrow	Myocardial necrosis
				Narrow	Myocardial reperfusion injury
				Narrow	Myocardial stunning
				Narrow	Papillary muscle infarction
				Narrow	Post procedural myocardial infarction
				Narrow	Postinfarction angina
				Narrow	Silent myocardial infarction
				Narrow	Troponin I increased
				Narrow	Troponin increased
				Narrow	Troponin T increased
				Broad	Blood creatine phosphokinase abnormal

				Broad	Blood creatine phosphokinase increased
				Broad	Cardiac ventricular scarring
				Broad	ECG electrically inactive area
				Broad	ECG signs of myocardial infarction
				Broad	Electrocardiogram Q wave abnormal
				Broad	Electrocardiogram ST segment abnormal
				Broad	Electrocardiogram ST segment elevation
				Broad	Electrocardiogram ST-T segment elevation
				Broad	Infarction
				Broad	Myocardial necrosis marker increased
				Broad	Scan myocardial perfusion abnormal
				Broad	Vascular graft occlusion
				Broad	Vascular stent occlusion
				Broad	Vascular stent thrombosis
Shock (SMQ)					
	Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)				
				Narrow	Acute left ventricular failure
				Narrow	Adams-Stokes syndrome
				Narrow	Atrial parasystole
				Narrow	Cardiac arrest
				Narrow	Cardiac arrest neonatal
				Narrow	Cardiac death
				Narrow	Cardiac fibrillation
				Narrow	Cardiac flutter
				Narrow	Cardiogenic shock
				Narrow	Cardio-respiratory arrest
				Narrow	Cardio-respiratory arrest neonatal
				Narrow	Cardiovascular insufficiency
				Narrow	Circulatory collapse
				Narrow	Obstructive shock
				Narrow	Pulse absent
				Narrow	Pulseless electrical activity
				Narrow	Shock
				Narrow	Shock symptom
				Narrow	Sudden cardiac death
				Narrow	Ventricular asystole
				Narrow	Ventricular fibrillation
				Narrow	Ventricular flutter
				Narrow	Ventricular parasystole
				Broad	Acute kidney injury
				Broad	Acute prerenal failure
				Broad	Acute respiratory failure

				Broad	Anuria
				Broad	Blood pressure immeasurable
				Broad	Cerebral hypoperfusion
				Broad	Grey syndrome neonatal
				Broad	Hepatic congestion
				Broad	Hepatojugular reflux
				Broad	Hepatorenal failure
				Broad	Hypoperfusion
				Broad	Jugular vein distension
				Broad	Myocardial depression
				Broad	Neonatal anuria
				Broad	Neonatal multi-organ failure
				Broad	Neonatal respiratory failure
				Broad	Organ failure
				Broad	Prerenal failure
				Broad	Propofol infusion syndrome
				Broad	Renal failure
				Broad	Renal failure neonatal
				Broad	Respiratory failure
Torsade de pointes/QT prolongation (SMQ)					
				Narrow	Electrocardiogram QT interval abnormal
				Narrow	Electrocardiogram QT prolonged
				Narrow	Long QT syndrome
				Narrow	Long QT syndrome congenital
				Narrow	Torsade de pointes
				Narrow	Ventricular tachycardia
				Broad	Cardiac arrest
				Broad	Cardiac death
				Broad	Cardiac fibrillation
				Broad	Cardio-respiratory arrest
				Broad	Electrocardiogram repolarisation abnormality
				Broad	Electrocardiogram U-wave abnormality
				Broad	Loss of consciousness
				Broad	Sudden cardiac death
				Broad	Sudden death
				Broad	Syncope
				Broad	Ventricular arrhythmia
				Broad	Ventricular fibrillation
				Broad	Ventricular flutter
				Broad	Ventricular tachyarrhythmia

APPENDIX 4: EQ-5D VALUATION INDEX - US

Please refer the following link:

http://www.euroqol.org/news-list/article/interim-scoring-for-the-eq-5d-5l-eq-5d-5l-crosswalk-index-value-calculator.html

APPENDIX 5: PREDEFINED MAJOR PROTOCOL DEVIATIONS

The predefined major protocol deviations of this study are described in the Protocol Deviation Criteria document. The deviations that may affect the assessment of efficacy are a subset of the predefined major protocol deviations and are indicated with 'Yes' in the Exclude from Per Protocol Analysis' column. For some major PDs as indicated a case-by-case evaluation will be performed as to whether the assessment of efficacy will be affected.

Sequence No.	Description	Protocol Deviation Coded Term (DVDECOD)	Protocol Deviation Term (DVTERM)	*Check/Listing *Medical listing **Source docs	Exclude from PP (i.e. with a major PD that might impact efficacy)	Classification/Remarks
INCLUSION CRITERIA (Subjects must meet the below inclusion criteria)						
1	Man or a woman between 18 and 70 years of age, extremes included.	Entered but did not satisfy criteria	Inclusion criterion 1 not met .	Checks/listings	**Case-by-case evaluation**	Major ***Note:*** For Singapore, age limit starts at 21 years due to local regulations
2	BMI of 18.0 to 35.0 kg/m2, extremes included.	Entered but did not satisfy criteria	Inclusion criterion 2 not met	Checks/listings	**Case-by-case evaluation**	Major
3	Documented chronic HCV infection: diagnosis of HCV infection >6 months before the first screening assessment.	Entered but did not satisfy criteria	Inclusion criterion 3 not met	Source Docs	**No**	Major
4	HCV genotype 1, 2, 4, 5 or 6 infection, determined at screening.	Entered but did not satisfy criteria	Inclusion criterion 4.1 not met	Checks/listings	**Yes**	Major If the subject has Genotype 3 then it should be recorded in exclusion
5	HCV RNA plasma levels >10 000 IU/mL at screening.	Entered but did not satisfy criteria	Inclusion criterion 6 not met	Checks/listings	**Yes**	Major Note: Retesting of laboratory values that lead to exclusion will be allowed once during the screening phase to assess eligibility
6	Either be HCV treatment-naïve, or treatment-experienced. Tx experienced defined as having received HCV therapy consisting of IFN (pegylated or non-pegylated) with or without RBV.	Entered but did not satisfy criteria	Inclusion criterion 7.1 not met	Checks/listings Source Docs	**Yes**	Major As these situations may need clinical assessment, the monitors are requested to provide details of the case to Quintiles Medical Monitor/SRP to confirm the criterion is met.
7	Female subjects of childbearing potential must have a negative serum (β-human chorionic gonadotropin) pregnancy test at screening.	Entered but did not satisfy criteria	Inclusion criterion 8 not met	Checks/listings	**No**	Major

Sequence No.	Description	Protocol Deviation Coded Term (DVDECOD)	Protocol Deviation Term (DVTERM)	*Check/Listing *Medical listing **Source docs	Exclude from PP (i.e. with a major PD that might impact efficacy)	Classification/Remarks
8	Female subjects must -either be not of childbearing potential or must be postmenopausal for at least 12 months (i.e., 2 years of amenorrhea without an alternative medical cause) and a serum follicle stimulating hormone (FSH) level in the postmenopausal range (>40 IU/mL), OR - be surgically sterile (have had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation/bilateral tubal clips without reversal operation), or otherwise be incapable of pregnancy. Or - be of childbearing potential and not heterosexually active (e.g., abstinence) from screening until 12 weeks after the EOT (or longer, if dictated by local regulations) Or have a vasectomized partner (confirmed sterile per verbal account of the subject),Or if heterosexually active, be participating an acceptable method of birth control from screening and agree to continue to use the same method of contraception throughout the study and for at least 12 weeks after the EOT (or longer, if dictated by local regulations).	Entered but did not satisfy criteria	Inclusion criterion 9.2 not met	Checks/Listings	**No**	Major Oral hormone-based contraceptives are not allowed from 14 days before baseline until 4 weeks after the EOT Note: The FSH level will be tested in female subjects who are postmenopausal for less than 2 years
9	The subject must be willing and able to comply with the protocol requirements, including the	Entered but did not satisfy criteria	Inclusion criterion 10 not met	Checks/Listings	**Case-by-case evaluation**	Major

Sequence No.	Description	Protocol Deviation Coded Term (DVDECOD)	Protocol Deviation Term (DVTERM)	*Check/Listing *Medical listing **Source docs	Exclude from PP (i.e. with a major PD that might impact efficacy)	Classification/Remarks
	Prohibitions and Restrictions described in Section 4.3					

Sequence No.	Description	Protocol Deviation Coded Term (DVDECOD)	Protocol Deviation Term (DVTERM)	*Check/Listing *Medical listing **Source docs	Exclude from PP (i.e. with a major PD that might impact efficacy)	Classification/Remarks
10	Subject must agree not to participate in other clinical studies for the duration of their participation in this study, except for observational studies and only after prior approval of the sponsor.	Entered but did not satisfy criteria	Inclusion criterion 11 not met	Source Docs	**Yes**	Major
11	Subject must voluntarily sign an ICF as such indicating that he or she understands the purpose of and procedures required for the study and is willing to participate in the study.	Entered but did not satisfy criteria	Inclusion criterion 12 not met .	Checks/listings	**No**	Major If an ICF is updated to include new data and was not read and signed by the patient, the deviation to be evaluated before classifying as major or not. This applies to main ICF and/or DNA ICF and/or consent form for PK sub study in Omega 1
12	The subject should have documented "Absence of Cirrhosis". "Absence of Cirrhosis" is defined by the following results: • Fibroscan with a result of ≤12.5 kPa within 6 months of baseline/Day 1, or • Liver biopsy within 6 months of baseline/Day 1 showing absence of cirrhosis (METAVIR score of F0-F3 or Ishak score <5	Entered but did not satisfy criteria	Inclusion criterion 13.1 not met	Checks/listings	**Yes**	Major Note: Liver biopsy should only be considered as an alternative in subjects where Fibroscan is not feasible
13	Female subject must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 12 weeks after the EOT.	Entered but did not satisfy criteria	Inclusion criterion 14 not met	Source Docs	**No**	Major
14	Female subjects must have a negative highly sensitive urine pregnancy test at Day 1.	Entered but did not satisfy criteria	. Inclusion criterion 15 not met	Checks/listings	**No**	Major

Sequence No.	Description	Protocol Deviation Coded Term (DVDECOD)	Protocol Deviation Term (DVTERM)	*Check/Listing *Medical listing **Source docs	Exclude from PP (i.e. with a major PD that might impact efficacy)	Classification/Remarks
15	Male subject must be surgically sterile (had a vasectomy), or otherwise incapable of fathering a child. Or Male subject must be not heterosexually active (eg, abstinence) from enrollment (Day 1) until at least 12 weeks after the EOT Or Male subject if heterosexually active has a partner who is postmenopausal (at least 12 months or until 2 years or more of amenorrhea), surgically sterile (has had a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation/bilateral tubal clips without reversal operation), or otherwise incapable of becoming pregnant Or Male subject if heterosexually active with a woman of childbearing potential, be practicing an acceptable method of birth control, as defined in protocol Inclusion Criterion 16, from enrolment in the study (Day 1) throughout the study and for at least 12 weeks after the EOT (or longer, if dictated by local regulations).	Entered but did not satisfy criteria	Inclusion criterion 16 not met	Checks/Listings	**No**	Major
16	Male subjects must agree not to donate sperm during the study until 12 weeks after the EOT (or longer, if dictated by local regulations)	Entered but did not satisfy criteria	Inclusion criterion 17 not met .	Source Docs	**No**	Major
EXCLUSION CRITERIA						
17	Subject has co-infection with multiple HCV genotypes,	Entered but did not satisfy criteria	Exclusion criterion 1 met	Checks/Listings (External Data Transfer)	**Yes**	Major

Sequence No.	Description	Protocol Deviation Coded Term (DVDECOD)	Protocol Deviation Term (DVTERM)	*Check/Listing *Medical listing **Source docs	Exclude from PP (i.e. with a major PD that might impact efficacy)	Classification/Remarks
18	Subject has co-infection with HIV	Entered but did not satisfy criteria	Exclusion criterion 2 met	Checks/listings	**Yes**	Major Absence of any inclusion/exclusion lab data is considered a major deviation
19	Presence of cirrhosis	Entered but did not satisfy criteria	Exclusion criterion 3.1 met	Checks/Listings	**Yes**	Major
20	Subject has prior exposure to an HCV DAA, either in combination with PegIFN or IFN-free,	Entered but did not satisfy criteria	Exclusion criterion 4 met	Source Documents	**Yes**	Major Note: This is applicable only for HCV treatment-experienced subjects
21	Subject has evidence of liver disease of non-HCV etiology (exclusion criterion 5).	Entered but did not satisfy criteria	Exclusion criterion 5 met	Source Documents Medical review listing	**No**	Major
22	Subject has evidence of liver disease of non-HCV etiology (exclusion criterion 5.1).	Entered but did not satisfy criteria	Exclusion criterion 5.1 met	Source Documents Medical review listing	**No**	Major Note: Canada-specific criterion
23	Subject has evidence of hepatic decompensation (history or current clinical evidence of ascites, bleeding varices or hepatic encephalopathy).	Entered but did not satisfy criteria	Exclusion criterion 6 met	Source Documents Medical review listing	**Yes**	Major
24	Subject has taken/used any disallowed therapies as noted in Section 8.	Entered but did not satisfy criteria	Exclusion criterion 7 met	Source Documents/ Check-listing/ Medical Review Listing	**Case-by-case evaluation**	Major
25	Subject has a history of malignancy within 5 years before screening (refer to CTP for exceptions).	Entered but did not satisfy criteria	Exclusion criterion 8 met .	Source Documents Medical review listing	**No**	Major
26	Subject has known allergies, hypersensitivity, or intolerance to AL-335, ODV, or SMV or their excipients .	Entered but did not satisfy criteria	Exclusion criterion 9 met	Source Documents	**No**	Major
27	Subject has presence of significant co-morbidities, conditions or clinically significant findings during	Entered but did not satisfy criteria	Exclusion criterion 10 met .	Source Documents	**No**	Major

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	screening for which, in the opinion of the investigator, participation would not be in the best interest of the subject.					

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28	Subject was a recipient of an organ transplant (check CTP for exception).	Entered but did not satisfy criteria	Exclusion criterion 11 met	Source Documents	**No**	Major
29	History or other clinical evidence of significant cardiac findings or conditions such as: □ cardiac disease (eg, angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia, coronary heart disease, moderate or severe valvular disease or uncontrolled hypertension) at screening; □ screening echocardiogram left ventricular ejection fraction (LVEF) <55% or any other echocardiogram finding suggestive of clinically relevant cardiomyopathy; □abnormal electrocardiogram (ECG) findings such as: significantly abnormal PR [PR interval >200 milliseconds], QRS intervals or corrected QT interval [QTc] >450 milliseconds for male subjects and >470 milliseconds for female subjects □ evidence of any heart block; □ evidence of right bundle branch block or left bundle branch block; □ history or family history of prolonged QT syndrome (torsade depointes) or sudden cardiac death.	Entered but did not satisfy criteria	Exclusion criterion 12 met	Source Documents Check-listing	**No**	Major

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30	Any of the following laboratory abnormalities at screening: □ Platelet count <75 x 10^3/µL or <75 x 10^9/L; □ Hemoglobin <11 g/dL or <6.83 mmol/L for male subjects, <10 g/dL or <6.21 mmol/L for female subjects; □ Absolute neutrophil count <1.00 x 10^3/µL or <1.00 x 10^9/L; □ Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >10 x upper limit of normal (ULN); □ Total serum bilirubin >1.5 x ULN; □ Albumin <3.5 g/dL or <35 g/L; □ Estimated glomerular filtration rate (eGFR) of <50 mL/min/1.73 m² .	Entered but did not satisfy criteria	Exclusion criterion 13 met	Source Docs + Check Listing	**No**	Major Note: Retesting of laboratory values that lead to exclusion will be allowed once during the screening phase to assess eligibility
31	Subject has other abnormal screening laboratory results that are considered clinically significant by the investigator.	Entered but did not satisfy criteria	Exclusion criterion 14 met	Source Docs	**No**	Major
32	Current or past abuse of alcohol or recreational or narcotic drugs, which in the investigator's opinion would compromise the subject's safety and/or compliance with the study procedures.	Entered but did not satisfy criteria	Exclusion criterion 15 met	Source Docs	**No**	Major Urine will be tested at screening to check the current use of amphetamines, benzodiazepines, cannabinoids, opioids and cocaine. Subjects with a positive drug test may only be included after consultation with the sponsor. Documentation of the investigator's assessment with regard to the subject's safety and compliance must be in place prior to the start of treatment.

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33	Pregnant, planning on becoming pregnant (during treatment and up to 12 weeks after the EOT), or breast-feeding female subject, or male subject whose female partner is pregnant or planning on becoming pregnant.	Entered but did not satisfy criteria	Exclusion criterion 16 met	Source Docs	**No**	Major
34	Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned first dose of study drug.	Entered but did not satisfy criteria	Exclusion criterion 17 met	Source Docs Medical Listings	**Yes**	Major
35	Subject has findings suggestive of hepatocellular carcinoma.	Entered but did not satisfy criteria	Exclusion criterion 18.1 met	Source Docs Checks/Listings	**Yes**	Major
36	Subjects with HCV genotype 3 infection.	Entered but did not satisfy criteria	Exclusion Criterion 19 met	Checks/Listings	**Yes**	Major
WITHDRAWAL CRITERIA (Treatment withdrawal)						
37	The investigator believes that for safety reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment.	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from study treatment even after investigator confirmed that the subject should discontinue study treatment for safety reasons <specify reason>	Source Document/Medical review Listing	**No**	Major
38	The subject becomes pregnant.	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from study treatment although the subject is pregnant. Or	Check/Listing	**No**	Major
39	The subject has a grade 3 rash	Developed treatment withdrawal	Subject was not withdrawn from the SMV treatment although a	Check/Listing	**No**	Major ODV and AL-335 treatments can continue with discretion of the investigator

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		criteria but not withdrawn	Grade 3 rash occurred			

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40	The subject has a grade 4 rash	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from study treatment although a grade 4 rash occurred	Check/Listing	**No**	Major
41	The subject has a grade 3 or 4 allergic reaction	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from study treatment although a <specify "grade 3" or "grade 4" allergic reaction occurred >	Medical review Listing/check - Listing	**No**	Major As these situations may need clinical assessment, the monitors are requested to provide details of the case to study physician (s) to confirm the deviation before filing a Major Deviation form.
42	The subject has a confirmed grade 4 ALT and/or AST value that is >2 times the baseline value;	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from study treatment although Grade 4 AST or ALT value greater than 2 times baseline value was confirmed	Medical Listing/Lab alerts/	**No**	Major Confirmatory measurement to be done within 72 hours after receipt of the results.
43	The subject has a confirmed grade 4 bilirubin value which is considered a sign of worsening liver disease, or for which there is no identifiable explanation	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from study treatment, although subject had a confirmed grade 4 bilirubin value considered a sign of worsening liver disease or for which there is no other identifiable explanation.	Medical Listing/Listing	**No**	Major Confirmatory measurement within 72 hours after receipt of the results.
44	For concurrent grade 4 ALT and/or AST elevations >2 times the baseline value and grade 4 bilirubin values, subjects should have a confirmatory measurement within 72 hours after receipt of the results. In case of confirmed grade 4 elevations, the study drugs should be discontinued.	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from study treatment, although For concurrent grade 4 ALT and/or AST elevations >2 times the baseline value and grade 4 bilirubin values, subjects should have a confirmatory measurement within 72 hours after receipt of the results. In case of confirmed grade 4 elevations, the study drugs should be discontinued	Medical Listing/Listing	**No**	Major

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45	The subject has severe worsening of hepatic disease	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from the study treatment although the subject experienced a severe worsening of hepatic disease.	Source document/Medical Listing	**No**	Major As these situations may need clinical assessment, the monitors are requested to provide details of the case to Study physician (s) to confirm before filing a Major Deviation form.
46	The subject has a confirmed grade 4 pancreatic amylase or lipase elevations, with confirmed presence of signs consistent with pancreatitis.	Developed treatment withdrawal criteria but not withdrawn	The study treatment wasn't interrupted although subject has a confirmed grade 4 pancreatic amylase or lipase elevations, or the presence of signs consistent with pancreatitis.	Source document/Medical Listing	**No**	***Major***
47	The subject has clinical signs suggestive of muscle injury	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from the study treatment although the subject has clinical signs suggestive of muscle injury	Source document/Medical Listing	**No**	Major
48	If CK is ≥20 × ULN, , AL-335 should be discontinued. Continuation of ODV and SMV should be discussed with the sponsor on a case-by-case basis	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from the study treatment although the CK is ≥ 20 X ULN	Source document/Medical Listing	**No**	Major
49	For asymptomatic subjects with no clinical evidence of congestive heart failure: Subject has a decrease in LVEF ≥10% from baseline and resulting in an LVEF of <50%,	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from the study treatment although the subject has a decrease in LVEF ≥ 10% from baseline and resulting in an LVEF of <50%,	Source Documents	**No**	*Major*

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50	Subject is symptomatic and has an absolute decrease in LVEF ≥5% from baseline	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from the study treatment although the subject has Symptoms and absolute decrease in LVEF ≥5% from baseline	Source Documents	**No**	*Major*
51	Subject has a PR interval of >300 ms	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from ODV treatment although the subject had a PR interval of >300 ms.	Source Documents	**No**	*Major*
52	Subject has a second degree or higher AV block.	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from ODV treatment although the subject had a second degree or higher AV block.	Checks/Listings	**No**	Major ODV to be stopped; AL-335 and SMV can continue at investigator discretion
53	Subject has QTc value of >500 milliseconds	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from The ODV treatment although the subject had QTc value of >500 milliseconds	Checks/Listings	**No**	Major
54	Subject has a confirmed eGFR <30 mL/min,	Developed treatment withdrawal criteria but not withdrawn	Study treatment was not interrupted although subject had a confirmed eGFR <30 mL/min	Checks/Listings	**No**	Major
55	The subject has a grade 4 AE at least possibly related to one of the study drugs	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from Study treatment although the subject has grade 4 AE at least possibly related to one of the study drugs.	Listings	**No**	Major

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56	Subject meets treatment stopping rule for viral breakthrough, but continued study treatment.	Developed treatment withdrawal criteria but not withdrawn	Subject was not withdrawn from the study treatment although subject meets treatment stopping rule for viral breakthrough at <specify visit>.	Medical Review Listings/lab alerts	**No**	Potentially Major .If continues treatment for > 14 days after confirmation to stop all study Medications.
DOSAGE & ADMINISTRATION						
57	The dose of SMV and/or AL-335 and/or ODV was not according to protocol.	Received wrong treatment or incorrect dose	Please update to "Subject received wrong dose of <specify study medication> (includes overdose or suboptimal dose).	Checks/Listings	**Yes**	potentially Major Dose adjustments are not allowed. . Consult SRP for case evaluation
58	AL-335, and/or ODV, and/or SMV intake was temporarily interrupted (either individual or two or all three study drugs) for more than 3 consecutive days	Received wrong treatment or incorrect dose	<Specify AL-335, ODV, and/or SMV> were temporarily interrupted for <specify duration> days.	Checks/Listings	**Yes**	Potentially Major Restart of medications to be done only after consultation with Sponsor.
59	Subject was dosed without being randomized.	Received wrong treatment or incorrect dose	Subject was dosed without being randomized.	Checks/Listings	**Yes**	Major
CONCOMITANT MEDICATION						
60	The subject takes/has taken disallowed medication as defined per protocol.	Subject used Disallowed medication.	Subject not compliant on the disallowed concomitant treatment	Medical review listing	**Case-by-case evaluation**	Potentially Major. As these situations may need clinical assessment, the monitors are requested to provide details of the case to the PK Expert and Study physician(s) to confirm

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OTHER – STUDY PROCEDURES						
61	A standard laboratory test (not specified as eligibility related labs) was not performed during screening period, but the subject was administered at least 1 dose of the study medication.	Other	<Specify test, e.g. "Blood sugar"> not performed at screening, but subject entered the trial.	Checks/Listings	**No**	Potentially Major
62	The subject missed two or more consecutive planned visits in the trial.	Other	Subject missed <specify visit> visit	Checks/Listings	**Case-by-case evaluation**	Potentially Major Missing visits with no preceding or post visit data to carry forward leading to lack of data will be considered major. Consultation with Study physician (s) is required to confirm
63	Subject continued to take study treatment after withdrawal of consent from the trial.	Other	Subject continued to take study treatment after withdrawal of consent from the trial.	Checks/Listings	**No**	Potentially Major
64	Subject had a screening period beyond 6 weeks and no safety re-screening was done.	Other	The randomization was done out of time window <specify timing>.	Checks/Listings	**No**	Potentially Major Screening may be extended beyond 6 weeks on a case-by-case basis after discussion with the sponsor.
65	Site reported protocol deviation not specified elsewhere.	Other	Site reported protocol Deviation not specified elsewhere: <specify>.	Checks/Listings	**No**	Potentially Major
66	Pharmacokinetic blood sample was not collected	Other	Pharmacokinetic blood sample was not collected	Checks/Listings	**No**	Potentially Major
67	Subject completed paper questionnaire instead of ePRO	Other	Subject completed paper questionnaire instead of ePRO	Checks/Listings	**No**	Potentially Major