

Janssen Research & Development ***Clinical Protocol**

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
AMENDMENT 4
AL-335, odalasvir, TMC435 (simeprevir)**

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	18 March 2016
Amendment 1	17 June 2016
Amendment 2	12 August 2016
Amendment 3	3 February 2017
Amendment 4	This document

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (10 April 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: This amendment is being written to implement study treatment stopping rules upon Health Authority feedback. In addition, as more subjects have been recruited than originally planned for, the actual number of subjects enrolled in the study is added and statistical considerations for safety are adjusted accordingly. Language with regard to HBV DNA assessments in subjects who are anti-HBc positive at baseline is added, references to a re-treatment study are deleted, changes are made to the statistical methods section and to the definitions of on-treatment failure and relapse.

Rationale: Following Health Authority feedback, treatment stopping rules for all subjects (study treatment stopping rules) are added to the protocol.

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 ejection fraction (EF) by ≥ 10 points with absolute EF $< 50\%$;
- a cardiac event that is serious, severe or life-threatening;

will lead to stop of dosing in all subjects in the current study if the event is adjudicated by the DRC to have met the above criteria and 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 72 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.

[1.3.2.2 Potential Risks](#)

[1.3.3 Overall Benefit/Risk Assessment](#)

[6.4 Study Treatment Stopping Rules](#)

[9.8.6.7 Cardiac Safety Monitoring](#)

[10.2 Discontinuation of Study Treatment](#)

[11.11 Data Review Committee](#)

Rationale: Recruitment for this Phase 2 HPC2001 study started in November 2016 and was completed as planned on 14 March 2017. Screening of new patients was stopped on 23 February 2017. As the screening failure rate towards the end of recruitment was significantly lower as compared to earlier observations, 365 patients were enrolled versus the approximately 300 patients planned. Per Sponsor's policy, patients still in screening at the time of reaching the target enrollment in the study are allowed to enroll when proven eligible after completion of the screening procedures. The Sponsor confirms the overall risk benefit balance of the study, the study hypothesis and the integrity of the study data in terms of both efficacy and safety remain unaltered.

As the actual subject recruitment exceeds 10% of the number of subjects planned for in the protocol dated 3 February 2017, it was deemed appropriate to report this subject number and to update the statistical methods section for safety to reflect the actual number of enrolled subjects.

SYNOPSIS

3.1 Overview of Study Design

4 SUBJECT POPULATION

11.2 Sample Size Determination

Rationale: References to possible re-treatment with AL-335 + ODV + SMV + ribavirin (RBV) for 12 weeks has been removed from the protocol since recently published robust data on re-treatment of DAA failures using soon-to-be-approved regimens have led to the decision not to conduct this re-treatment study. For all subjects who do not achieve SVR, the sponsor will reimburse one treatment regimen with the standard of care for this population in the respective country.

1.3.2.2 Potential Risks

1.3.3 Overall Benefit/Risk Assessment

3.1 Overview of Study Design

Rationale: Following the recent review of direct-acting antivirals carried out by the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) on returning signs and symptoms of previously inactive hepatitis B infection (re-activation) when patients were treated with direct-acting antivirals (DAAs) for hepatitis C, the PRAC recommended to include a warning in the prescribing information about hepatitis B reactivation and how to minimize it. This recommendation has now been endorsed by EMA's Committee for Medicinal Products for Human Use (CHMP).

HBsAg positive subjects are excluded from the current study. At baseline an anti-HBc test is performed in all subjects, but subjects with a positive test can be included in the study. In order to better monitor the risk of HBV reactivation during or following short-term HCV DAA treatment, language is added to the protocol indicating the need to measure HBV DNA in subjects with a clinically relevant ALT flare as defined in Section 9.8.6.3.

TIME AND EVENTS SCHEDULE

9.8.6.3 Alanine Aminotransferase, Aspartate Aminotransferase and Bilirubin Elevations

Rationale: Since the sponsor's clinical development strategy aims to establish the shortest efficacious treatment duration, a fixed sequence procedure for adjusting for multiple confidence intervals will be used to determine non-inferiority of the treatment regimens compared to a historical control and not the Dunnett's test as indicated in Section 11.3 of the protocol (dated 3 February 2017). The 6-week treatment will be tested first (at two-sided alpha of 5%) and only if this is statistically non-inferior, the 8-week treatment will be tested for non-inferiority also at two-sided alpha of 5%. The protocol has been adjusted accordingly.

11.3 Efficacy Analyses

Rationale: The definition of on-treatment failure and viral relapse are adjusted to align with Health Authority guidance on the development of direct-acting antivirals (DAAs) for the treatment of HCV infection.

DEFINITIONS OF TERMS

Rationale: Minor errors were corrected.

SYNOPSIS**ABBREVIATIONS****TIME AND EVENTS SCHEDULE**

3.1 Overview of Study Design

4.1 Inclusion Criteria

9.8.6.6 Creatine Kinase

9.8.6.7 Cardiac Safety Monitoring

11.2 Sample Size Determination

Amendment 3 (3 February 2017)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: This amendment is being written to adjust the concomitant medication section of the protocol.

Rationale: The protocol dated 12 August 2016 disallows the use of concomitant medication with a potential to prolong QT interval. Reference is made to the comprehensive list of drugs associated with QT prolongation and/or Torsades de Pointes (QT Drug Lists by Risk Groups) provided by the Arizona Center for Education and Research on Therapeutics³⁷ from screening until the end of the study. This amendment is being written to update Section 8 PRESTUDY AND CONCOMITANT THERAPY in order to incorporate the possibility to enroll subjects on stable treatment with a drug that has the potential to prolong QT interval under specified conditions.

Available data from 26-week nonclinical studies showed that dose levels at which there were no cardiac findings corresponded to safety margins of ~6-fold for a 25-mg qd dose at steady state (6,930 ng·h/mL) in humans (predicted for the combination with 800 mg AL-335 and 75 mg SMV). In addition, available clinical data have not indicated an effect of AL-335, ODV or SMV on QTc. Hence, the sponsor does not consider the risk-benefit of the study altered by allowing eligible HCV infected patients on a stable concomitant drug with a potential to increase QT interval under specified conditions.

The protocol will continue to disallow the start of medications with the potential to prolong QT interval from screening until the end of the study unless the medication is necessary to protect subject safety and it has been discussed with the sponsor.

1.3.2.2 Potential Risks

8 PRESTUDY AND CONCOMITANT THERAPY

Amendment 2 (12 August 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: Change in design of the Phase 2b study with focus on treatment-naïve and treatment-experienced HCV genotype 1, 2, 4, 5 or 6 infected subjects without cirrhosis.

Rationale: Following Health Authority feedback, the sponsor has decided to focus this Phase 2b study on HCV genotype 1, 2, 4, 5 and 6 infected subjects without cirrhosis for the evaluation of the efficacy, safety and pharmacokinetics of 6- and 8-week treatment with AL-335, odalasvir (ODV) and simeprevir (SMV).

In addition, stratification factors are adjusted. Randomized subjects 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). In the stratification by HCV geno/subtype, subjects with a genotype 1 non-specifiable subtype at screening will be assigned to the genotype 1b, 4, 5 or 6 stratification group.

The sample size remains unchanged, ie, 300 subjects (150 subjects/arm).

TITLE PAGE

SYNOPSIS

TIME AND EVENTS SCHEDULE

1.1.2 Treatment of HCV Infection

1.4 Overall Rationale for the Study

2.1 Objectives

3.1 Overview of Study Design

3.2 Study Design Rationale

4 SUBJECT POPULATION

4.1 Inclusion Criteria

4.2 Exclusion Criteria

5 TREATMENT ALLOCATION AND BLINDING

9.1.2 Screening Phase

9.2.2.3 Exploratory Endpoints

Rationale: Following Health Authority feedback, more detail on nonclinical cardiac toxicology data is added. In addition, preliminary data from an 8-week mechanistic oral gavage toxicity and toxicokinetic study with ODV in telemetered dogs are added. Based on the nonclinical cardiac toxicity data, the potential risk section for ODV described in Section 1.3.2.2 is updated.

1.1.4 Background of Odalasvir

1.3.1 Known Benefits and Risks

1.3.2.2 Potential Risks

1.3.3 Overall Benefit/Risk Assessment

Rationale: Data of studies AL-335-602 and AL-335-604 are updated with final data from study AL-335-602 and preliminary data from study AL-335-604, in line with the AL-335 Investigator's Brochure Edition 2, Addendum 2⁴³ and the ODV Investigator's Brochure Edition 6, Addendum 4.⁴⁴ The preliminary data from study AL-335-604 are based on a snapshot analysis, ie, no formal database lock was performed.

ABBREVIATIONS

1 INTRODUCTION

1.1.3 Background of AL-335

1.1.4 Background of Odalasvir

1.2 Background to All-oral Combination Regimens

1.3.2.2 Potential Risks

1.4 Overall Rationale for the Study

3.2 Study Design Rationale

REFERENCES

Rationale: It is clarified in the protocol that safety, efficacy, and/or pharmacokinetic data from this study may be pooled with data from the Phase 2a AL-335-604 study and potentially other similarly performed studies to assess the combination regimen of AL-335, ODV and SMV. This will increase the sample size for the different subgroups/duration groups and provide for more accurate estimates for safety and efficacy endpoints. The details of this combined analysis will be outlined in a separate analysis plan.

3.1 Overview of Study Design

11 STATISTICAL METHODS

Rationale: Following Health Authority feedback, the recommendations regarding the concomitant use of calcium channel blockers are modified, ie, these drugs are disallowed from screening until the end of the study. Per the protocol Amendment 1, dated 17 June 2016, the concomitant use of calcium channel blockers without known impact on QT interval was to be used with caution. The sponsor in addition decided to disallow the use of sodium and potassium channel blockers from screening until the end of the study.

The list of proton-pump inhibitors, antifungals and antiretrovirals was extended.

It was clarified that consumption of large quantities of grapefruit juice (>1 liter/day) is disallowed from baseline till the end of treatment.

8 PRESTUDY AND CONCOMITANT THERAPY

Rationale: Following recent publications on the reactivation of HBV infection after short duration DAA-containing HCV treatment^a, the sponsor decided to add anti-HBc testing at baseline to the protocol. For anti-HBc positive subjects, anti-HBs will be determined.

TIME AND EVENTS SCHEDULE

9.8.2 Clinical Laboratory Tests

Rationale: The protocol is aligned with the recently updated sponsor's internal protocol template with regard to the prohibitions and restrictions, including location of contraceptive requirement. In addition, the language of the contraceptive requirements is being aligned across the planned/ongoing JNJ-64294178 studies and adjusted in this protocol accordingly.

^a Ende AR, Kim NH, Yeh MM, Harper J, Landis CS. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. *Journal of Medical Case Reports*. 2015;9: 1-4.

Collins JM, Rapael KL, Terry C, et al. Hepatitis B virus reactivation during successful treatment of hepatitis C virus with sofosbuvir and simeprevir. *Clinical Infectious Diseases*. 2015;61(8): 1304-1306.

Kimura H, Ohkawa K, Sakakibara M et al. Sustained hepatitis C virus RNA clearance accompanied by elevation of hepatitis B virus DNA after short-term peginterferon-alpha, ribavirin and simeprevir therapy in chronic hepatitis patient having dual infection with hepatitis B and C viruses. *Acta Hepatologica Japonica*. 2015;56(8): 422-427.

Balagopal A, Thio CL. Another call to cure Hepatitis B. *Clinical Infectious Disease*. 2015;61(8): 1307-1309.

Sato T. A case of superinfection of HBV/HCV in which therapy with daclatasvir and asunaprevir was done. The 103rd Cyugoku Regional Meeting of the Japanese Society of Gastroenterology. 2015;56.

1.3.2.2 Potential Risks

4.1 Inclusion Criteria

4.3 Prohibitions and Restrictions

8 PRESTUDY AND CONCOMITANT THERAPY

Rationale: A sentence was added to the protocol to clarify that all efforts need to be made to enroll as many HCV genotype 2, 4, 5 and 6 infected subjects as possible.

SYNOPSIS

3.1 Overview of Study Design

4 SUBJECT POPULATION

Rationale: The list of anticipated events included in Attachment 8 has been updated.

ATTACHMENTS

Rationale: The time window for the Fibroscan confirming absence of cirrhosis has been adjusted from within 3 months prior to baseline/Day 1 to within 6 months prior to baseline/Day 1.

SYNOPSIS

TIME AND EVENTS SCHEDULE

4.1 Inclusion Criteria

Rationale: Minor errors and inconsistencies were noted and corrected and clarifications were added where required.

SYNOPSIS

TIME AND EVENTS SCHEDULE

1.1.2 Treatment of HCV Infection

1.1.3 Background of AL-335

1.1.4 Background of Odalasvir

1.1.5 Background of Simeprevir

1.2 Background to All-oral Combination Regimens

1.3.1 Known Benefits and Risks

1.3.2.2 Potential Risks

1.3.3 Overall Benefit/Risk Assessment

1.4 Overall Rationale for the Study

3.1 Overview of Study Design

3.2 Study Design Rationale

4.2 Exclusion Criteria

4.3 Prohibitions and Restrictions

8 PRESTUDY AND CONCOMITANT THERAPY

9.3.1 Evaluations

9.3.3 Pharmacokinetic Parameters

9.8.2 Clinical Laboratory Tests

9.8.6.7 Cardiac Safety Monitoring

11.11 Data Review Committee

REFERENCES

Amendment 1 (17 June 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: Change in design of the Phase 2b study with focus on evaluating the 3-DAA treatment regimen comprising of AL-335+ODV with SMV.

Rationale: In treatment of chronic HCV infection, a combination of potent direct-acting antivirals (DAAs) with a different mechanism of action and non-overlapping resistance profiles is required to maximize the likelihood of achieving sustained virologic response (SVR) or cure. Currently, a Phase 2a study, AL-335-604, to evaluate the safety, pharmacokinetics and efficacy of the combination of AL-335, ODV and SMV in treatment-naïve subjects with genotype 1 and genotype 3 CHC is ongoing. In this Phase 2a study different treatment regimens of AL-335+ODV with or without SMV (2-DAA and 3-DAA regimen) are being studied with the aim to determine the optimal dose of each component. Preliminary data from the ongoing Phase 2a study AL-335-604 (refer to Section 1.2 for details) provide support for the use of the 3-DAA combination of AL-335+ODV with SMV to maximize SVR when evaluating short treatment durations of 6 and 8 weeks.

Based on the above data, the sponsor has made an informed decision to focus only on the 3-DAA combination. The updated study design of study 64294178HPC2001 aims to evaluate the combination of a 3-DAA regimen (AL-335 800 mg qd + ODV 25 mg qd + SMV 75 mg qd) in a regimen that shortens treatment duration compared to currently available treatment regimens, regardless of genotype or the presence or absence of compensated cirrhosis, to 8 or 6 weeks without compromising efficacy, or the subject's compliance and safety.

The 3-DAA regimen will be investigated for both 6 and 8 weeks (arms A and B). An increase in sample size per study arm from 100 to 150 patients will allow for more robust subgroup analysis. Sample size calculations were adjusted accordingly. The aim remains to have 30% of the subjects overall with compensated cirrhosis who are restricted to having genotype 1 or 3 infection. In addition, proportionally to the aim in the protocol dated 18 March 2016, per treatment arm, approximately 30 HCV genotype 3 infected subjects, including approximately 15 subjects with cirrhosis, are aimed to be enrolled.

As per the initial protocol of 18 March 2016, 20 subjects from the 2-DAA (arms C and D combined) and 20 subjects from the 3-DAA (arms A and B combined) arms were planned to be included in the sparse PK and rich PK substudies each. In correspondence with the initial protocol, 20 subjects from arms A and B combined will be included in the sparse and rich PK substudies, each. However, since the 2-DAA combination will not be studied (arms C and D) the total number of subjects in the sparse and rich PK substudies will be 20 subjects each compared to 40 subjects in the initial protocol.

SYNOPSIS**TIME AND EVENTS SCHEDULE**

- 1.1.2 Treatment of HCV Infection
- 1.2 Background to All-oral Combination Regimens
- 1.4 Overall Rationale for the Study
- 2.1 Objectives
- 3.1 Overview of Study Design
- 3.2 Study Design Rationale
- 4 SUBJECT POPULATION
- 4.3 Prohibitions and Restrictions
- 5 TREATMENT ALLOCATION AND BLINDING
- 6 DOSAGE AND ADMINISTRATION
- 6.1 Timing of Doses

8 PRESTUDY AND CONCOMITANT THERAPY

9.1.3 Open-label Treatment Phase

9.1.4 Post-treatment Phase (Follow-Up)

9.3.1 Evaluations

9.3.2 Analytical Procedures

9.3.3 Pharmacokinetic Parameters

9.8.6 Management of Specific Toxicities

11.2 Sample Size Determination

11.3 Efficacy Analyses

11.4 Pharmacokinetic Analyses

11.7 Occupational/Employment Status Analysis

11.8 Medical Resource Utilization

11.9 Safety Analyses

Rationale: Given the long half-life of ODV and to ensure close monitoring of patients for late relapse during follow-up an additional visit will be scheduled 18 weeks after the EOT to collect samples for HCV RNA determination and viral sequencing.

SYNOPSIS

TIME AND EVENTS SCHEDULE

9.2.2.2 Secondary Endpoints

Rationale: Following Health Authorities recommendation, it is clarified in the protocol that substantial changes to the study conduct other than the possible treatment prolongation triggered by the DRC which is clearly specified in the protocol, will lead to a protocol amendment which is to be submitted to ECs/IRBs for approval. In addition it is clarified that DRC also take emerging data of other completed and ongoing studies, including the Phase 2a study AL-335-604, into account in making informed recommendations on the continuation of the current study.

SYNOPSIS

1.3.3 Overall Benefit/Risk Assessment

3.1 Overview of Study Design

6.3 Treatment Stopping Rule (for Viral Breakthrough)

11.11 Data Review Committee

Rationale: Per the initial protocol of 18 March 2016, from the W4 FU visit until the subject's last study related procedure, only SAEs, AEs at least possibly related to the study drugs by the investigator and AEs leading to study discontinuation had to be reported. Following Health Authority feedback, the protocol is adjusted to indicate that all AEs, irrespective of severity or causality, need to be reported from signing of the ICF until the subject's last study visit. In addition, the assessment of AEs at Week 10 visit (if applicable) was missing in the Time and Events Schedule and has been added.

SYNOPSIS

TIME AND EVENTS SCHEDULE

1.3.3 Overall Benefit/Risk Assessment

9.1.4 Post-treatment Phase (Follow-Up)

9.8 Safety Evaluations

9.8.2 Clinical Laboratory Tests

9.8.3 Electrocardiogram and Echocardiography

9.8.4 Vital Signs

9.8.5 Physical Examination

12.3.1 All Adverse Events

Rationale: For female subjects of childbearing potential, a urine pregnancy test will be performed on Day 1 and at least every 4 to 6 weeks up to the W24 FU visit. The urine pregnancy test to be performed on Day 1 was not consistently mentioned throughout the protocol. This inconsistency is corrected. In addition, given the long half-life of ODV, urine pregnancy tests will be performed every 4 to 6 weeks up to the W24 FU visit and not up to the W12 FU visit as indicated in the initial protocol dated 18 March 2016.

TIME AND EVENTS SCHEDULE

4.3 Prohibitions and Restrictions

9.1.3 Open-label Treatment Phase

Rationale: Following Health Authority feedback, recommendations with regard to concomitant therapy with amiodarone has been changed, disallowing amiodarone within 3 months prior to screening until the end of the study rather than EOT as per the initial protocol, dated 18 March 2016. In addition, a note is added to indicate that all concomitant medications with a potential to prolong QT interval, including digoxin, are disallowed from screening until the end of the study. Reference is made to the comprehensive list of drugs associated with QT prolongation and/or Torsades de Pointes (QT Drug Lists by Risk Groups) provided by the Arizona Center for Education and Research on Therapeutics.³⁹ Consequently, medications with the potential to prolong QT interval were removed from the list of medications 'to be used with caution'. Finally, recommendations with regard to the use of grapefruit juice are added: consumption of large quantities of grapefruit juice (>1 liter/day) should be avoided from baseline till EOT.

8 PRESTUDY AND CONCOMITANT THERAPY

REFERENCES

Rationale: Following Health Authority recommendations, B-type natriuretic peptide (BNP) testing is added to the protocol. The addition of testing with BNP increases the possibility for early detection of impaired cardiac function in between evaluation with echocardiography. To this end, BNP assessment will be performed at baseline, Week 2, Week 4, Week 6, the EOT and Week 4 FU.

TIME AND EVENTS SCHEDULE

ABBREVIATIONS

8 PRESTUDY AND CONCOMITANT THERAPY

9.8.2 Clinical Laboratory Tests

Rationale: Following Health Authority feedback, more information is provided with regard to the potential risk of development of drug resistance.

1.3.2.2 Potential Risks

REFERENCES

Rationale: Following Health Authority feedback, the goal of the efficacy analyses is further clarified.

11.3 Efficacy Analyses

Rationale: Following Health Authority feedback, it is clarified that in case new information that may be relevant to the subject's willingness to participate in the study becomes available, the investigator should inform the subject and should ensure the subject signs a revised consent, if applicable. In addition, it is clarified that the sponsor will notify the concerned Health Authorities of any urgent safety measures and potential serious breaches in accordance with the sponsor's internal procedures and in line with the timelines defined in local regulations.

12 ADVERSE EVENT REPORTING

16.2.3 Informed Consent

Rationale: Following Health Authority feedback, the individual stopping criteria in response to changes in the EF described in Section 9.8.6.7 Cardiac Safety Monitoring of the protocol have been clarified. Asymptomatic patients with no clinical evidence of congestive failure: (1) if the absolute change (decrease) from baseline in LVEF $\geq 10\%$ (eg, 59% to 49%) should discontinue AL-335, ODV and SMV if the change results in an LVEF of $< 50\%$. If the change is $> 10\%$ but resulting in an LVEF $> 50\%$, an assessment of the subject's clinical status including symptoms, physical exam, and other clinical parameters should be made before deciding whether to stop or continue study drugs. In both cases a mandatory assessment and urgent cardiology referral should be planned; the LVEF decrease must be reported to the Medical Monitor within 24 hours so that the clinical case and workup and treatment strategy can be discussed.

9.8.6.7 Cardiac Safety Monitoring

Rationale: Taking into account the normal physiological variations that can be observed with regard to PR intervals, and considering that an isolated ECG finding of increased PR interval does not necessarily indicate an underlying pathological condition that impacts the overall benefit-risk assessment, the individual stopping criteria in response to changes in PR interval (described in Section 9.8.6.7 Cardiac Safety Monitoring) have been clarified:

- (1) If the PR interval is > 200 milliseconds but < 240 milliseconds, study drugs can be continued. Close monitoring with weekly ECGs is recommended;
- (2) If the PR interval > 240 milliseconds but < 300 milliseconds (confirmed by a repeat triplicate analysis at least 30 minutes after the initial assessment), an assessment of the subject's clinical status, including symptoms, physical exam, and other clinical parameters should be made and study drugs can be continued. Close monitoring with weekly ECG is recommended;
- (3) If the PR interval is > 300 milliseconds⁴³ or a 2nd degree or higher AV block is diagnosed (confirmed by a repeat triplicate analysis at least 30 minutes after the initial assessment and irrespective of presence or absence of clinical symptoms), ODV must be discontinued. AL-335 and SMV may be continued at the investigator's discretion.

Furthermore, it is specified in the protocol that, in case the QTc value is > 500 milliseconds (confirmed by a repeat triplicate analysis at least 30 minutes after the initial assessment and irrespective of presence or absence of clinical symptoms), ODV must be discontinued. AL-335 and SMV may be continued at the investigator's discretion. In case the QTc value increases by > 60 milliseconds from baseline, thorough evaluation of the clinical case and discussion with the sponsor is required to assess further treatment strategy.

9.8.6.7 Cardiac Safety Monitoring

Rationale: In the footnotes to the Time and Events Schedule, the timing of Fibroscan, liver biopsy and ultrasound were incorrect and inconsistent with the body text of the protocol. This is corrected to indicate that, in subjects with cirrhosis, cirrhosis should be confirmed by a Fibroscan or liver biopsy performed prior to or during the screening period. For subjects without cirrhosis, absence of cirrhosis should be confirmed by Fibroscan performed within 3 months or liver biopsy within 6 months of baseline (Day 1). Subjects with cirrhosis have to receive an ultrasound scan within 3 months prior to baseline/Day 1.

TIME AND EVENTS SCHEDULE

Rationale: According to the initial protocol, dated 18 March 2016, in certain cases of abnormal CK values all study medication had to be discontinued (see Section 9.8.6.6). However, since some subjects, depending on their baseline characteristics, may have a high chance of achieving SVR when they continue treatment with ODV and SMV, the sponsor considers it more appropriate to discontinue AL-335 and for the investigator to discuss ODV and SMV continuation with the sponsor on a case-by-case basis. Only if a subject who experiences CK elevations also demonstrates clinical or laboratory evidence of renal insufficiency/damage or other clinically significant muscle signs or symptoms (eg, proximal weakness), all study medication should be stopped regardless of the magnitude of the CK elevation.

9.8.6.6 Creatine Kinase

Rationale: It is specified that, if thyroid stimulating hormone (TSH) is not within the normal range, testing of free triiodothyronine (fT3) and free thyroxine (fT4) will be performed.

TIME AND EVENTS SCHEDULE

ABBREVIATIONS

9.8.2 Clinical Laboratory Tests

Rationale: For clarity, the terminology with regard to the PK sampling is made consistent throughout the protocol, ie, PK blood sampling for the samples taken in all subjects, rich serial PK substudy (N=20 subjects) and sparse PK substudy (N=20 subjects). In addition, the body of the protocol was made consistent with regard to the documentation of food intake on the days of PK assessments and the previous day, ie, on the day prior to the PK assessments (all PK samples) it will be recorded whether study drugs were taken with food (ie, during or no later than 15 minutes after a meal). In case of the PK sampling in all subjects and the sparse PK substudy, on the day of the PK sampling it will be recorded whether study drugs were taken with food (ie, during or no later than 15 minutes after a meal). In the rich serial PK substudy on the day of the PK sampling, the start and end time of the meal will be recorded.

SYNOPSIS

6.1 Timing of Doses

7 TREATMENT COMPLIANCE

9.1.3 Open-label Treatment Phase

9.1.4 Post-treatment Phase (Follow-Up)

9.3.1 Evaluations

11.4 Pharmacokinetic Analyses

Rationale: The protocol is aligned with the recently updated sponsor's internal protocol template.

4.1 Inclusion Criteria

16.2.2 Independent Ethics Committee or Institutional Review Board

17.5 Case Report Form Completion

Rationale: In Attachment 2, the toxicity grading table for vital sign parameters was erroneously copied where the table for the PR interval toxicity grading scale had to be provided. This error is corrected.

Attachment 2: Cardiovascular Safety - Abnormalities

Rationale: Minor errors were noted and corrected and minor clarifications were added where considered needed.

SYNOPSIS

TIME AND EVENTS SCHEDULE

1.1.2 Treatment of HCV Infection

1.1.3 Background of AL-335

- 1.3.1 Known Benefits and Risks
 - 1.3.3 Overall Benefit/Risk Assessment
 - 1.4 Overall Rationale for the Study
 - 2.1 Objectives
 - 3.1 Overview of Study Design
 - 3.2 Study Design Rationale
 - 4.1 Inclusion Criteria
 - 4.3 Prohibitions and Restrictions
 - 8 PRESTUDY AND CONCOMITANT THERAPY
 - 9.1.2 Screening Phase
 - 9.1.3 Open-label Treatment Phase
 - 9.1.4 Post-treatment Phase (Follow-Up)
 - 9.2.1.1 HCV RNA Levels
 - 9.2.1.3 Resistance Determinations
 - 9.3.1 Evaluations
 - 9.8.3 Electrocardiogram and Echocardiography
 - 9.8.6 Management of Specific Toxicities
 - 9.8.6.1 Rash (Including Photosensitivity Conditions)
 - 9.8.6.7 Cardiac Safety Monitoring
 - 10.2 Discontinuation of Study Treatment
 - 11.4 Pharmacokinetic Analyses
- REFERENCES
-

SYNOPSIS

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.

AL-335 (also known as JNJ-64146212) is a uridine based nucleoside monophosphate prodrug (or nucleotide analog) targeting hepatitis C virus (HCV) non-structural protein (NS)5B polymerase being developed for the treatment of chronic HCV (in clinical development).

Odalasvir (ODV, also known as ACH-0143102 and ACH-3102) is an HCV NS5A inhibitor being developed for the treatment of chronic HCV infection (in clinical development).

Simeprevir (SMV, also known as TMC435) is an HCV NS3/4A protease inhibitor approved for the treatment of chronic HCV genotype 1 and 4 infection.

OBJECTIVE AND HYPOTHESES

Primary Objective

To evaluate the efficacy, ie, sustained virologic response 12 weeks after the end of treatment (SVR12), of a combination treatment with AL-335, ODV, and SMV for 6 and 8 weeks in chronic HCV genotype 1, 2, 4, 5 and 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 [AUC_{24h}] and predose plasma concentrations [C_{0h}]) 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).

Hypothesis

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 antiviral [DAA] regimens) with a non-inferiority margin of 10%.

Statistical testing will be conducted using null hypothesis $H_0: C-T \geq 10\%$ vs. $H_a: C-T < 10\%$ at a significance level of 0.05, 2-sided, where C is the historical control rate of 98% and T is the expected SVR rate in the treatment arm.

OVERVIEW OF STUDY DESIGN

This is a Phase 2b multicenter, randomized, open-label, study to investigate the efficacy, safety and PK of a 6- and 8-week treatment regimen with AL-335, ODV, and SMV followed by a 24-week post-treatment follow-up in treatment-naïve and treatment-experienced subjects with chronic HCV genotype 1, 2, 4, 5 or 6 infection without cirrhosis.

The study will include a screening period of maximum 6 weeks starting from the time of the first screening assessment. In exceptional cases, the screening phase can be extended if discussed with and approved (documented) by the sponsor. Thereafter, if eligible, subjects will be randomized to receive AL-335, ODV, and SMV for either 6 or 8 weeks. A post-treatment follow-up until 24 weeks after the actual end of treatment (EOT) is included to assess SVR12 and SVR24. The total study duration for each subject will be approximately 36 to 38 weeks (including the 6-week screening period, the 6- or 8-week treatment period, and the 24-week post-treatment follow-up period). The study is considered completed with the last visit of the last subject participating in the study.

The dose of SMV will be 75 mg once daily (qd), the dose of ODV will be 25 mg qd, and the dose of AL-335 will be 800 mg qd.

Approximately 300 treatment-naïve or -experienced (to [pegylated {Peg}] IFN ± ribavirin [RBV]) chronic HCV genotype 1, 2, 4, 5 and 6 infected subjects without cirrhosis will be randomized (in a 1:1 ratio) to one of the following treatment arms:

- Arm A (N=150): AL-335 800 mg qd + ODV 25 mg qd + SMV 75 mg qd for 6 weeks
- Arm B (N=150): AL-335 800 mg qd + ODV 25 mg qd + SMV 75 mg qd for 8 weeks

Patients still in screening at the time of reaching the target enrollment in the study were allowed to enroll when proven eligible after completion of the screening procedures, leading to the enrollment of an additional 65 subjects in the study (365 subjects in total: 183 subjects in Arm A and 182 subjects in Arm B).

Randomized subjects in arms A and B will be stratified by HCV treatment history (treatment-naïve versus treatment-experienced) and HCV geno/subtype (genotype 1a or 2 versus genotype 1b, 4, 5, or 6). In the stratification by HCV geno/subtype, subjects with a genotype 1 non-specifiable subtype at screening will be assigned to the 1b, 4, 5 or 6 stratification group. All efforts need to be made to enroll as many HCV genotype 2, 4, 5 and 6 subjects as possible.

HCV RNA levels will be processed in real time and continuously monitored by the sponsor and communicated to the investigator throughout the study. Subjects will be monitored from Day 1 through end of follow-up for viral breakthrough or relapse. Study drugs will be discontinued for subjects with viral breakthrough (ie, confirmed $>1.0 \log_{10}$ increase in HCV RNA from nadir or confirmed HCV RNA >100 IU/mL in subjects who had previously achieved HCV RNA $<$ lower limit of quantification [LLOQ]).

A Data Review Committee (DRC) will be established to monitor data on a regular basis to ensure the continuing safety, efficacy, and well-being of the subjects enrolled in this study. The DRC is a committee within the sponsor's organization that is independent of the sponsor's study team. Virologic failures will be communicated immediately to the DRC to trigger efficacy review. Emerging safety and efficacy data from this study will be reviewed at predetermined intervals. As a part of the safety evaluations, the DRC will also review adverse events (AEs) considered as anticipated events for this patient population.

Upon review of the HCV RNA data from this study and/or consideration of data from other completed and ongoing studies, including the Phase 2a study AL-335-604, the DRC will make study conduct recommendations, which may include but are not limited to, continuing the study without modifications and/or implementation of treatment extension as described below. The sponsor's decision based on the recommendation will be communicated to the investigator. Details will be specified in a separate charter.

In case a treatment extension is recommended by the DRC, treatment duration of the arms will be extended up to a maximum of 12 weeks (ie, the 6-week arm will be extended to 8 weeks, or both arms will be extended to 12 weeks). All subjects will continue to attend study visits every 2 weeks. In case of treatment extension to 8 weeks, the subjects should follow the visit schedule of subjects initially included in the 8-week treatment arm, with an EOT visit at Week 8. In case of treatment extension to 12 weeks, subjects should follow the schedule for the 12-week treatment extension arm with an EOT visit at Week 12 (see [Time and Events Schedule](#)).

In case of substantial changes to the study conduct, other than the treatment extension described above, an amendment to the current protocol will be submitted for approval by the competent authorities.

If study drug treatment is discontinued prematurely, for reasons other than withdrawal of consent, a treatment withdrawal visit should be scheduled as soon as possible after the EOT. The subjects will be followed-up for 24 weeks after EOT, with visits as indicated in the [Time and Events Schedule](#). If a subject discontinues treatment due to withdrawal of consent, the subject will be offered an optional early treatment withdrawal visit, to be scheduled as soon as possible after withdrawal and/or a safety follow-up visit, which needs to be scheduled 4 weeks after EOT. At the safety follow-up visit safety assessments of the Week 4 follow-up (W4 FU) visit need to be performed. Any subject who withdraws consent during

the follow-up phase and/or notifies the site he or she will not return for study visits, will be invited to do a follow-up visit at the time of withdrawal to complete the full set of protocol procedures as scheduled for the Week 24 follow-up (W24 FU) visit. However, all possible efforts should be made to ensure that subjects complete the study.

SUBJECT POPULATION

Approximately 300 subjects were planned to be enrolled in the study and in total 365 subjects have been enrolled. The first screening assessment will be performed within 6 weeks before the first administration of study drugs. The key inclusion and exclusion criteria are summarized below.

Key Inclusion Criteria	Description
Age and sex	Man or woman, 18 to 70 years of age, inclusive.
Body Mass Index	Body Mass Index (BMI) of 18.0 to 35.0 kg/m ² , inclusive.
HCV genotype	All subjects must have HCV genotype 1, 2, 4, 5 or 6 infection, determined at screening.
Plasma HCV RNA	>10,000 IU/mL (determined at screening).
HCV treatment history	Subjects can either be HCV treatment-naïve, defined as not having received treatment with any approved or investigational drug (including DAAs, IFN-based treatments, and vaccines) for chronic HCV infection, or HCV treatment-experienced, defined as having received HCV therapy consisting of IFN (pegylated or non-pegylated) with or without RBV.
Absence of cirrhosis	Subjects without cirrhosis (absence of cirrhosis) defined as any of the following: <ul style="list-style-type: none"> • 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). • <p><i>Note: liver biopsy should only be considered as an alternative in subjects where Fibroscan is not feasible.</i></p>
Key Exclusion Criteria	Description
Infection/co-infection	HCV genotype 3 infection HCV co-infection with multiple genotypes Human immunodeficiency virus (HIV) co-infection Presence of cirrhosis
Exposure to a DAA	Prior exposure to an HCV DAA, either in combination with PegIFN or IFN-free.
Liver disease of non-HCV etiology	Any evidence of liver disease of non-HCV etiology. This includes, but is not limited to, acute hepatitis A infection (immunoglobulin M), hepatitis B infection (hepatitis B surface antigen positive), drug- or alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, primary biliary cirrhosis, or any other non-HCV liver disease that is considered clinically significant by the investigator.
Hepatic decompensation	Evidence of hepatic decompensation (history or current clinical evidence of ascites, bleeding varices or hepatic encephalopathy).
Organ transplant	Subjects who were recipients of an organ transplant (other than cornea or hair transplant or skin graft).

Cardiac-related medical history	<p>History or other clinical evidence of significant cardiac findings or conditions such as:</p> <ul style="list-style-type: none"> 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 (based on the average of the 3 QTc values used to determine the subject's eligibility); 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 de pointes) or sudden cardiac death.
Key laboratory values	<p>Any of the following laboratory abnormalities at screening:</p> <ul style="list-style-type: none"> Platelet count <75 x 10³/μL or <75 x 10⁹/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 10³/μL or <1.00 x 10⁹/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.
Hepatocellular carcinoma	Subjects who have findings suggestive of hepatocellular carcinoma.

DOSAGE AND ADMINISTRATION

All subjects will receive AL-335 800 mg qd, ODV 25 mg qd, and SMV 75 mg qd for 6 weeks (arm A) or 8 weeks (arm B).

All study drugs (AL-335, ODV, and SMV) should be taken once daily together in the morning at approximately the same time every day throughout the treatment phase and should be taken with food (ie, during or no later than 15 minutes after a meal).

EFFICACY EVALUATIONS

All evaluations will be performed as specified in the [Time and Events Schedule](#).

HCV RNA Levels

Blood samples for the determination of HCV RNA levels will be taken at all scheduled visits, processed in real time and results closely monitored by the sponsor. The results will be communicated to the investigator throughout the study.

ALT and AST

ALT and AST levels will be determined as part of the biochemistry panel of the clinical laboratory tests. Samples for biochemistry will be taken at predefined time points and will be processed in real time.

Resistance Determinations

Sequencing of the HCV NS3/4A, NS5A and NS5B regions will be performed to identify pre-existing sequence polymorphisms and characterize emerging HCV variants. The NS3/4A, NS5A and NS5B

regions will be sequenced pre-treatment (from the baseline sample) by default in all subjects and post-baseline in subjects not achieving SVR. Sequencing of additional samples may be triggered by the sponsor virologist.

Patient-reported Outcomes

The impact of HCV and its treatment (safety and efficacy) on patient-reported symptoms, functioning and HRQoL will be evaluated, in all subjects at selected sites where appropriate translations are available, at predefined time points. The following PRO assessments will be used: CLDQ-HCV, EQ-5D-5L, FSS, and SF-36v2 questionnaire.

PHARMACOKINETIC EVALUATIONS

All subjects will undergo PK blood sampling at the Week 4 visit, the Week 6 visit (arm B), and at the EOT visit at any time during the visit for the measurement of plasma concentrations of AL-335 (and metabolites), ODV, and SMV (see the [Time and Events Schedule](#)). At the EOT visit, subjects should still be on treatment at the time of the PK assessment. In case of treatment extension to 8 weeks or 12 weeks, no additional PK assessments will be done.

In the rich serial PK substudy and sparse PK substudy, performed at selected study sites, PK blood sampling for the measurement of plasma concentrations of AL-335 (and metabolites), ODV, and SMV will be performed in approximately 20 subjects in the rich PK substudy and 20 subjects in the sparse PK substudy, as indicated in the [Time and Events Schedule: PK Assessments in PK Substudies](#).

PHARMACOKINETIC/PHARMACODYNAMIC EVALUATIONS

Relationships of AL-335 (and metabolites), ODV, and SMV population-derived exposure parameters (C_{0h} and AUC_{24h}) with SVR12 and with safety endpoints will be explored graphically.

PHARMACOGENOMIC EVALUATIONS

One mandatory blood sample for host *IL28B* genotyping will be collected at the baseline visit, providing the opportunity to explore the influence of a genetic polymorphism upstream of the *IL28B* gene (rs12979860) on treatment outcome to the drug regimen assessed in this study. Where locally permitted and upon consent of the subject (in addition to the consent for the main part of the study) an additional optional blood sample will be collected at baseline for exploratory host deoxyribonucleic acid (DNA) research related to AL-335 (and metabolites), ODV, and SMV, and limited to genes involved in the metabolism of the study drugs as well as drug transporter genes.

OCCUPATIONAL/EMPLOYMENT STATUS

Information regarding occupational/employment status will be collected for all subjects at predefined time points.

MEDICAL RESOURCE UTILIZATION

MRU data will be collected at all scheduled visits from baseline until the W24 FU visit. Data collected may be used to conduct exploratory economic analyses.

SAFETY EVALUATIONS

Safety and tolerability will be evaluated throughout the study from signing of the informed consent form (ICF) onwards until the end of the study. The evaluations of safety and tolerability will include monitoring of adverse events (AEs), clinical laboratory tests, ECGs, echocardiograms, vital sign measurements and physical examinations at predefined time points.

All AEs, whether serious or non-serious as well as pregnancies, will be reported from the time a signed ICF is obtained until the subject's last study visit.

Specific toxicity management plans in line with the known pharmacological profile of the study drugs (and the drug class) evaluated in this study are incorporated in this protocol.

STATISTICAL METHODS

The description of the sizing for the study based on 300 subjects is provided 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 confidence interval (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%).

In addition, with a total sample size of 150 subjects in each treatment arm (300 subjects in total), the probability to observe an adverse event (AE) with an incidence of 0.1%, 0.5%, 0.8%, and 1% are 13.9% (25.9%), 52.9% (77.8%), 70.0% (91.0%), and 77.9% (95.1%), respectively.

To aid in the evaluation of efficacy of the 3-DAA regimens, Bayesian posterior probabilities on the true SVR will be calculated using uninformative prior (Jeffreys prior) and provided to the DRC. The posterior probability that the true SVR exceeds certain thresholds (eg, 90%, 95%) will be generated. Posterior probabilities associated with alternative thresholds may also be provided and are intended to aid the DRC in the interim evaluations of efficacy. Similar computations may also be provided for safety endpoints of interest.

In conclusion, a total sample size of 300 subjects in the study is considered sufficient to explore the efficacy, safety, tolerability and PK of the 3-DAA regimen in this study.

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 a probability to observe an 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.

The primary efficacy analyses will be performed on the intent-to-treat (ITT) population, defined as all subjects who received at least one dose of study drugs (AL-335, ODV, or SMV).

Additional sensitivity analyses on efficacy may be performed after excluding subjects with early treatment discontinuation due to non-virologic reasons or missing data at the SVR12 time point, as well as on the per-protocol population, defined as the ITT population excluding subjects with a pre-specified major protocol deviation.

An interim analysis is planned at the SVR4 time point, ie, when all subjects have reached the SVR4 (Week 4 follow-up visit [W4 FU visit]) time point or discontinued earlier.

The primary analysis will be performed when all subjects have reached the SVR12 time point (W12 FU visit) or discontinued earlier. Additional interim analyses may be conducted if needed to support clinical development.

The final analysis will be performed when all subjects have completed the last study-related visit (SVR24 time point; W24 FU visit) or discontinued earlier.

A DRC will be established to monitor data of the current study on a regular basis to ensure the continuing safety, efficacy and well-being of the subjects enrolled in the study. The DRC will take into consideration the data from the current study as well as data from completed and ongoing studies, including the Phase 2a study AL-335-604 in their recommendations regarding the continuation of the study.

Efficacy Analyses

The primary efficacy endpoint is:

- The proportion of chronic HCV infected subjects who achieve SVR12.

For the definition of SVR12, see the Definitions of Terms.

The secondary efficacy endpoints are:

- The proportion of subjects with SVR4 and SVR24,
- The proportion of subjects with viral relapse,
- The proportion of subjects with on-treatment failure,
- The proportion of subjects with virologic response:
 - HCV RNA <lower limit of quantification (LLOQ) undetectable,
 - HCV RNA <LLOQ,
- Time to achieve undetectable HCV RNA and HCV RNA <LLOQ,
- The effect of the presence or absence at baseline of NS3/4A, NS5A, or NS5B polymorphisms on treatment outcome,
- The changes from baseline in amino acid sequence in the HCV NS3/4A, NS5A and NS5B regions in subjects not achieving SVR,
- The relationship between the population-derived exposure parameters of SMV (AUC_{24h} and C_{0h}) with SVR12 and safety,
- Change from baseline over time in mean score for each of the following PRO scores:
 - EQ-5D-5L: VAS score,
 - FSS: Total score,
- The proportion of subjects with clinically important improvement from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in FSS total and EQ-5D-5L VAS scores,
- The time to clinically important improvement from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in FSS total and EQ-5D-5L VAS,
- The proportion of subjects with clinically important worsening from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in FSS total and EQ-5D-5L VAS,
- The duration (weeks) of clinically important worsening from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in FSS total and EQ-5D-5L VAS,

- Change from baseline over time in EQ-5D-5L VAL score and Domain scores.

For definitions of on-treatment virologic response, SVR4, SVR24, on-treatment failure and viral relapse, see the Definitions of Terms.

For the primary endpoint, for each treatment arm, the proportion of subjects who achieve SVR12 will be calculated. A 2-sided 95% CI will be constructed around the SVR12. The lower limit of the 95% CI of the SVR12 rate will be compared against the performance benchmark for non-inferiority. A lower bound of the 2-sided 95% CI $\geq 88\%$ will satisfy the hypothesis for non-inferiority in at least one treatment arm.

Additional sensitivity analysis may be performed by applying different imputation rules for missing data. Missing data patterns will be analyzed and described in detail.

To aid in the evaluation of efficacy of the 3-DAA regimens, Bayesian posterior probabilities on the true SVR will be calculated using uninformative prior.

Descriptive statistics will be used for all efficacy endpoints and will be tabulated by treatment arm.

The potential association between treatment outcome and baseline factors such as stratification factors, geno/subtype, and baseline HCV RNA levels will be explored by subgroup analysis.

Resistance Determination Analyses

The results of viral sequencing will be evaluated by the sponsor virologist. Pre-treatment polymorphisms in the HCV NS3/4A, NS5A and NS5B regions in all subjects and relevant changes in the HCV NS3/4A, NS5A and NS5B regions in subjects not achieving SVR will be tabulated and described. The effect of pre-treatment NS3/4A, NS5A and NS5B polymorphisms on treatment outcome will be explored.

Patient-reported Outcomes Analyses

Patient-reported outcomes scores will be analyzed descriptively by treatment arm as mean scores over time, and evaluated based on the proportion of subjects experiencing a clinically important improvement or worsening in PRO scores from baseline during study drug treatment and follow-up. Time and duration of clinically important significant improvement or worsening in PRO scores will be analyzed and reported.

Pharmacokinetic Analyses

The PK samples taken from all subjects in the study (see [Time and Events Schedule](#)), as well as the sparse and rich PK samples collected in the PK substudies ([Time and Events Schedule: PK Assessments in PK Substudies](#)) will be used for population PK (popPK) model development and/or popPK model update. PopPK analysis of plasma concentration-time data of AL-335 (and its metabolites), ODV, and SMV from all subjects (including those of sparse and rich PK substudies) will be performed using nonlinear mixed-effects modeling. Population PK modeling will be used to describe the concentration-time profiles and estimate the exposure parameters (AUC_{24h} and C_{0h}) of AL-335 (and its metabolites), ODV, and SMV. Available baseline subject characteristics (demographics, body weight, laboratory variables, genotype, etc.) may be explored as potential covariates affecting PK parameters of AL-335, ODV, or SMV. Details will be given in a popPK analysis plan and the results of the popPK analysis will be presented in a separate popPK report.

For the intensive PK samples of the rich PK substudy, non-compartmental PK analysis of AL-335 (and its metabolites), ODV, and SMV will be performed using actual sampling time and plasma concentrations obtained from rich serial PK blood sampling at Week 4 for approximately 20 subjects (arms A and B combined). Descriptive statistics will be provided for the PK parameters derived, including graphical analyses of the data.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of AL-335 (and metabolites), ODV, and SMV population-derived exposure parameters (AUC_{24h} and C_{0h}) with SVR12 and with safety endpoints will be explored. These relationships will be presented in a graphical display.

Pharmacogenomic Analyses

Baseline *IL28B* genotyping data will be tabulated. Subgroup analyses will be done to explore the effect of the *IL28B* genotype (rs12979860) on efficacy by means of descriptive statistics and frequency tabulations.

The statistical approach for analyzing the exploratory host DNA research may depend on the objective of the analyses (treatment response, side effects, metabolism) and possibly relevant genes at the time of analysis.

Occupational/Employment Status Analysis

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

Medical Resource Utilization

MRU data will be descriptively summarized by treatment arm over time.

Safety Analyses

The incidence of AEs will be summarized for each treatment arm by body system and preferred term. Changes from baseline in clinical laboratory values, vital signs, ECG parameters, and key echocardiography parameters (including LVEF) will be presented descriptively. The percentage of subjects with abnormal clinical laboratory, vital sign, ECG parameter, and LVEF values will be presented by treatment arm. Physical examination findings will be listed.

TIME AND EVENTS SCHEDULE

Phase	Screening ^a	Baseline ^b	Treatment Phase ^{c,d}											Post-Treatment Follow-Up Phase					
			W-6	D1	D2	D3	W1	W2	W3	W4	W6 ^f	(W8) ^{g,ff}	(W10) ^{ff}	EOT ^h	Early treatment withdrawal visit ^e	W4 FU	W8 FU	W12 FU	W18 FU
Study Procedures																			
Screening/Administrative																			
Informed consent form (ICF) ^j	X																		
Demographics	X																		
Medical/surgical history	X																		
Prestudy therapies	X																		
Concomitant diseases	X																		
Inclusion/exclusion criteria	X	X ^k																	
Hepatitis C virus (HCV) geno-/subtyping	X																		
Fibroscan/biopsy ^l	X																		
Echocardiography ^m	X							X							X				
Electrocardiogram (ECG) ^m	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Pregnancy test ⁿ	X	X						X		X		X ^o	X	X	X	X	X	X	X
Follicle-stimulating hormone (FSH) ^p	X																		
Hepatitis A, B and C serology ⁱⁱ	X	X																	
Human immunodeficiency virus (HIV) type 1 and 2 serology	X																		
Study Drug Administration																			
Provision of study drugs for daily use at home		X						X		X ^{ff}									
Study drugs to be taken		X				X		X					X						

Phase	Screening ^a	Baseline ^b	Treatment Phase ^{c,d}											Post-Treatment Follow-Up Phase					
			W-6	D1	D2	D3	W1	W2	W3	W4	W6 ^f	(W8) ^{g,ff}	(W10) ^{ff}	EOT ^h	Early treatment withdrawal visit ^e	W4 FU	W8 FU	W12 FU	W18 FU
Study Procedures																			
on-site																			
Provision of medication diary		X																	
Collection and review of medication diary, and review of used or unused study drugs			X	X	X	X	X	X	X	X	X	X	X	X					
Adherence counseling		X	X	X	X	X	X	X	X	X	X	X	X						
Efficacy Assessments																			
HCV RNA determination ^f	X	X ^q	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral sequencing ^s		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient-reported outcomes (PROs) ^t		X						X					X	X ^u	X		X		X
Occupational/Employment Status																			
Occupational/employment status		X						X		X		X	X	X	X	X	X		X
Medical Resource Utilization (MRU)																			
MRU		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics (PK)																			
Plasma concentrations of AL-335 (and metabolites), odalasvir (ODV), and simeprevir (SMV) ^v								X	X ^f				X ^w						
Sparse PK substudy - plasma concentrations of AL-335 (and metabolites), ODV, and SMV	See Time and Events Schedule: PK Assessments in PK Substudies																		
Rich PK substudy - plasma concentrations of AL-335 (and metabolites),	See Time and Events Schedule: PK Assessments in PK Substudies																		

Phase	Screening ^a	Baseline ^b	Treatment Phase ^{c,d}											Post-Treatment Follow-Up Phase					
			W-6	D1	D2	D3	W1	W2	W3	W4	W6 ^f	(W8) ^{g,ff}	(W10) ^{ff}	EOT ^h	Early treatment withdrawal visit ^e	W4 FU	W8 FU	W12 FU	W18 FU
Study Procedures																			
ODV, and SMV																			
Safety Assessments																			
Physical examination ^x																			
Vital signs ^y																			
Clinical Laboratory Assessments																			
Hematology, biochemistry ^{jj}																			
Urinalysis																			
Pharmacogenomics (blood sample)																			
Host interleukin-28B (<i>IL28B</i>) genotyping																			
Host DNA research ^{dd}																			
Ongoing Subject Review																			
Concomitant therapy																			
Adverse events (AEs) ^{cc}																			

FU: follow-up

- ^a The first screening assessment has to be performed within 6 weeks prior to the baseline visit. Retesting of values (eg, safety laboratory or HCV RNA) that lead to exclusion will be allowed once during the screening phase to assess eligibility. Any potential delays in the screening phase will be discussed with the sponsor and evaluated on a case-by-case basis.
- ^b All baseline assessments need to be performed before study drug intake, except for a second blood sample on Day 1 for post-dose HCV RNA determination, which should be taken within 4 hours after dosing.
- ^c Subjects should ensure intake of study drugs exactly up to 6 weeks (43 days) or 8 weeks (57 days) of treatment (or 12 weeks [85 days] of treatment in case of treatment extension to 12 weeks), depending on the treatment arm they are in, in order to complete the indicated treatment duration.
- ^d In case a treatment extension is recommended by the DRC, subjects will continue to attend study visits every 2 weeks. In case of treatment extension to 8 weeks, the subjects should follow the visit schedule of subjects initially included in the 8-week treatment arm, with an EOT visit at Week 8. In case of treatment extension to 12 weeks, subjects should follow the schedule for the 12-week treatment extension arm. Subjects should ensure intake of study drugs exactly up to 8 weeks (57 days) or 12 weeks (85 days) of treatment, depending on the extended treatment duration, in order to complete the indicated treatment duration.

- ^e If study drug treatment is discontinued prematurely, for reasons other than withdrawal of consent, a treatment withdrawal visit should be scheduled as soon as possible after the EOT. The subjects will be followed-up for 24 weeks after EOT, with visits as indicated in the [Time and Events Schedule](#). If a subject discontinues treatment due to withdrawal of consent, the subject will be offered an optional early treatment withdrawal visit, to be scheduled as soon as possible after withdrawal and/or a safety follow-up visit, which needs to be scheduled 4 weeks after EOT. At the safety follow-up visit safety assessments of the W4 FU visit need to be performed.
- ^f The Week 6 assessments should not be performed if the Week 6 is the EOT visit (arm A); in that case only the EOT assessments should be performed.
- ^g The Week 8 assessments should not be performed if the Week 8 is the EOT visit (arm B); in that case only the EOT assessments should be performed.
- ^h In case of the treatment extension of the 6-week treatment arm to 8 weeks, the EOT assessments will be performed at Week 8. In case of treatment extension of the 6-week and/or 8-week treatment arms to 12 weeks, the EOT assessments will be performed at Week 12.
- ⁱ Any subject who withdraws consent during the follow-up phase and/or notifies the site he or she will not return for study visits, will be invited to do a follow-up visit at the time of withdrawal to complete the full set of protocol procedures as scheduled for the Week 24 follow-up visit. However, all possible efforts should be made to ensure that subjects complete the study.
- ^j Signing of the ICF can be done before the screening visit but needs to be done before the first study-related activity.
- ^k Investigator to confirm eligibility based on the overall clinical picture.
- ^l Absence of cirrhosis confirmed by Fibroscan performed within 6 months or liver biopsy within 6 months of baseline (Day 1). A biopsy should only be considered in subjects who do not have access to Fibroscan at the study site or at a referral site.
- ^m Additional ECG, echocardiography or cardiac monitoring may be done at any time during the study if clinically indicated in the opinion of the investigator. The subject will be instructed to rest in the supine position for 5 minutes before having an ECG assessment performed. If blood sampling or vital signs are scheduled at the same time point as the ECG recording, the procedures should preferably be performed in the following order: ECG, vital signs and blood draw.
- ⁿ For women of childbearing potential, a serum pregnancy test will be performed at screening and a urine pregnancy test is to be performed on-site on Day 1 and every 4 to 6 weeks up to the W24 FU visit.
- ^o A urine pregnancy test is not needed at the EOT visit for female subjects in the 6-week treatment arm, since they had a urine pregnancy test within 2 weeks prior to the EOT visit, ie, at Week 4.
- ^p FSH will be tested for female subjects who are postmenopausal for less than 2 years.
- ^q Two blood samples need to be taken: a first sample pre-dose and a second sample post-dose but within 4 hours after dosing. The time when the pre- and post-dose blood sample is obtained as well as the timing of the dosing at baseline should be recorded.
- ^r During follow-up, suspected relapse, ie, HCV RNA \geq LLOQ after previous $<$ LLOQ, needs to be confirmed preferably within 2 weeks after the result has become available, and this retest may require an unscheduled visit which should be scheduled by the investigator.
- ^s Viral sequencing will be performed on baseline samples by default in all subjects and on post-baseline samples in subjects not achieving sustained virologic response (SVR). Sequencing of additional samples may be triggered by the sponsor virologist.
- ^t PRO assessments will be performed by all subjects at sites where appropriate translations are available. Subjects will complete the Chronic Liver Disease Quality of Life Questionnaire - HCV (CLDQ-HCV), 5-level EuroQol 5-Dimension (EQ-5D-5L), Fatigue Severity Scale (FSS), and Short Form 36 version 2 (SF-36v2) questionnaires on an electronic device during the specified clinic visits. The ePRO assessments are to be completed before **any** tests, procedures or other consultations for that visit to prevent influencing the subject's perceptions.
- ^u No PRO assessments need to be performed if a PRO assessment was performed within 2 weeks prior to the withdrawal visit.

- v A PK sample for popPK analysis will be collected in all subjects at any time during the visit. A PK sample is not needed at Week 4 for subjects participating in the rich serial PK substudy and at Week 6 for subjects participating in the sparse PK substudy (see [Time and Events Schedule: PK Assessments in PK Substudies](#)). For these subjects a PK sample is taken as part of the PK substudies.
- w At the EOT visit, subjects should still be on treatment at the time of the PK assessment (the last dose is expected to be taken on the morning of the visit).
- x Complete physical examination (including height, body weight and body systems) will be performed at screening (does not include breast, genitals or rectal examination unless considered necessary by the investigator based on the subject's past and present medical history). At all other time points, a targeted physical examination based on the medical history and overall clinical presentation (including body weight) will be performed.
- y Systolic and diastolic blood pressure and pulse/heart rate need to be taken supine after at least 5 minutes of rest.
- z Biochemistry samples must be taken after fasting for at least 8 hours. Lipid profile is only to be assessed during visits with fasting samples.
- aa An additional blood sample for biochemistry should be taken for assessment of insulin and glucose.
- bb Thyroid stimulating hormone (TSH) is to be assessed at screening and EOT or early withdrawal. In case TSH is not within the normal range, testing of free triiodothyronine (fT3) and free thyroxine (fT4) will be performed.
- cc Includes a urine drug screening test.
- dd An optional blood sample for exploratory host DNA research limited to genes involved in the metabolism of the study drugs as well as drug transporter genes may be taken where locally permitted and upon consent of the subject (in addition to the consent for the main part of the study).
- ee All adverse events (AEs), whether serious or non-serious, and pregnancies will be reported from the time a signed ICF is obtained until the subject's last study visit.
- ff Only applicable in case of treatment extension to 12 weeks.
- gg Includes assessment of B-type natriuretic peptide (BNP).
- hh Assessment of BNP only.
- ii At screening, determination of HBsAg should be performed to determine eligibility of the subjects. At baseline, a blood sample should be taken for determination of anti-HBc. For anti-HBc positive subjects, anti-HBs will be determined. Hepatitis A and C serology will only be determined at screening.
- jj Any significant ALT flare during the conduct of the study, defined as either: (1) ALT of >2X ULN and >2X the lowest previous ALT value measured during the study, OR (2) any treatment-emergent grade 3 ALT elevation (>5X ULN), will trigger a thorough clinical work-up of the case by the investigator. This evaluation should include the assessment of serum HBV DNA (mandatory in subjects that are anti-HBc antibody positive at baseline).

Time and Events Schedule: PK Assessments in PK Substudies**Rich serial PK substudy^a (N~20)**

Time of Visit	Sampling Time (hours)										
	pre-dose	dosing	1h	2h	3h	4h	6h	8h	10h	12h	24h
Week 4 ^{b,c}	X (-0.5h)			X	X	X	X	X	X	X	X

^a This may require an overnight stay in the hospital.

^b Study drugs should be taken on site.

^c One of the assessments can be used as the PK assessment scheduled at Week 4 (to be taken anytime during the visit) indicated in the main [Time and Events Schedule](#); no additional sample is needed.

Sparse PK substudy (N~20^a)

Time of Visit	Sampling Time (hours)										
	pre-dose	dosing	1h	2h	3h	4h	6h	8h	10h	12h	24h
Week 2 ^b	X				X (anytime between 2h and 4h post-dose)						
After 6 weeks of treatment ^c EOT visit ^{c,d} (arm A) Week 6 ^d (arm B)							X (anytime between 6h and 12h post-dose)				
After 8 weeks of treatment ^c EOT visit ^{b,c} (arm B)	X			X (anytime between 2h and 4h post-dose)							
W4 FU, W12 FU, W 24 FU	Any time during the visit for ODV only										

^a Sparse PK sampling for AL-335 (and metabolites), ODV, and SMV will be performed in approximately 20 subjects (arms A and B combined) not participating in the rich serial PK substudy. At least 5 subjects are to be included from each arm.

^b Study drugs should be taken on site.

^c Subjects should still be on treatment at the time of the PK assessment.

^d This assessment can be used as the PK assessment scheduled at Week 6 (to be taken anytime during the visit) indicated in the main [Time and Events Schedule](#); no additional PK blood sample is needed.

^e In case of treatment extension to 8 weeks or 12 weeks, no additional PK assessments will be done.

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC _{24h}	area under the plasma concentration-time curve from time 0 to 24 hours after dosing
AV	atrioventricular
BCRP	breast cancer resistance protein
BMI	body mass index
BNP	B-type natriuretic peptide
BSEP	bile salt export pump
C _{0h}	predose (trough) plasma concentration
CI	confidence interval
CK	creatinine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CK-MB	creatinine kinase muscle-brain
CLDQ-HCV	Chronic Liver Disease Quality of Life Questionnaire – HCV
C _{max}	maximum plasma concentration
C _{min}	minimum plasma concentration
C _{trough}	trough plasma concentration
CYP	cytochrome P450
DAA	direct-acting antiviral agent
DCV	daclatasvir
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DRC	Data Review Committee
EC _{50/90}	50%/90% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EF	ejection fraction
(e)GFR	(estimated) glomerular filtration rate
EOT	end of treatment
(e)PRO	(electronic) patient-reported outcome
EQ-5D-5L	5-level EuroQol 5-Dimension
ft3	free triiodothyronine
ft4	Free thyroxine
FC	fold change
FSH	follicle-stimulating hormone
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HOMA-IR	homeostatis model assessment insulin resistance
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

IEC	Independent Ethics Committee
IFN	interferon
<i>IL28B</i>	interleukin-28B
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IVRS	interactive voice response system
IWRS	interactive web response system
LFC	liquid-filled capsule
LLOQ	lower limit of quantification
LVEF	left ventricular ejection fraction
MAD	multiple ascending dose
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MRP	multidrug resistance-associated protein
MRU	Medical Resource Utilization
NS	non-structural (protein)
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT2	organic cation transporter 2
ODV	odalasvir
PCS	physical component summary
PegIFN	pegylated interferon
P-gp	P-glycoprotein
pH	power of hydrogen
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
qd	once daily
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAV	resistance-associated variant
RBC	red blood cell
RBV	ribavirin
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SF-36v2	Short Form 36 version 2
SMV	simeprevir
SOF	sofosbuvir
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
SVRx	sustained virologic response <i>x</i> weeks after the end of treatment
$t_{1/2,term}$	terminal elimination half-life
t_{max}	time to reach maximum plasma concentration
TMC	Tibotec Medicinal Compound
TSH	thyroid stimulating hormone
ULN	upper limit of normal

VAS	Visual Analog Scale
VEL	velpatasvir
VI	Valuation Index
WBC	white blood cell
WHO	World Health Organization
WXFU	Week <i>X</i> Follow-up

DEFINITIONS OF TERMS

Study drugs:	AL-335, odalasvir (ODV), and simeprevir (SMV)
End of treatment (EOT)	Completion of dosing or premature discontinuation of treatment, whichever is earlier.
On-treatment Virologic Response	Subjects with hepatitis C virus (HCV) RNA <lower limit of quantification (LLOQ) undetectable or <LLOQ (detectable or undetectable) at specified time points during treatment.
Sustained Virologic Response (SVR X)	Subjects achieve SVR X if HCV RNA <LLOQ (detectable or undetectable) X weeks after EOT.
Failure (no SVR12)	Subjects who do not achieve SVR12, including: <ul style="list-style-type: none"> • on-treatment failure (see below) • post-treatment failure, including subjects with: <ul style="list-style-type: none"> - viral relapse (see below); - missing HCV RNA at time point of SVR12.
On-treatment Failure	Subjects who do not achieve SVR12, with confirmed HCV RNA \geq LLOQ at the actual EOT. Includes subjects with: <ul style="list-style-type: none"> • viral breakthrough, defined as a confirmed increase of $>1 \log_{10}$ in HCV RNA from nadir, or confirmed HCV RNA >100 IU/mL in subjects whose HCV RNA had previously been <LLOQ while on treatment. • other with confirmed HCV RNA \geqLLOQ at the actual EOT (eg, completed study drug treatment, discontinued due to AEs, withdrawal of consent).
Viral Relapse	Subjects who did not achieve SVR12, with HCV RNA <LLOQ at the EOT and confirmed HCV RNA \geq LLOQ during follow-up.
Late viral relapse	Subjects who achieved SVR12 but have confirmed HCV RNA \geq LLOQ afterwards during follow-up.
East-Asian subjects	East-Asian subjects are defined as subjects whose parents and maternal and paternal grandparents are Japanese, Chinese, Taiwanese or Korean, as determined by subject's verbal report.
<i>The following definition characterizes subject's HCV treatment experience:</i>	
Treatment-naïve	Subjects are considered treatment-naïve if they have never received treatment with any approved or investigational drug (including direct-acting antivirals [DAAs], interferon [IFN]-based treatments and vaccines) for chronic HCV infection.
Treatment-experienced	Subjects who have received at least one previous course of interferon (IFN; pegylated or non-pegylated) with or without ribavirin (RBV). Note that subjects with a history of treatment with an approved or investigational anti-HCV DAA are excluded.

1. INTRODUCTION

AL-335 (also known as JNJ-64146212) is a uridine based nucleoside monophosphate prodrug (or nucleotide analog) targeting hepatitis C virus (HCV) non-structural protein (NS)5B polymerase being developed for the treatment of chronic HCV (in clinical development).

Odalasvir (ODV, also known as ACH-0143102 and ACH-3102) is an HCV NS5A inhibitor being developed for the treatment of chronic HCV infection (in clinical development).

Simeprevir (SMV, also known as TMC435) is an HCV NS3/4A protease inhibitor approved for the treatment of chronic HCV genotype 1 and 4 infection.

For the most comprehensive nonclinical and clinical information regarding AL-335, ODV, and SMV, refer to the latest version of the Investigator's Brochure (IB) and Addenda, if applicable, for AL-335, ODV, and SMV, respectively.^{15,16,17,18,42,43,44}

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

1.1.1. HCV Infection

HCV infection is a leading cause of liver disease worldwide. An estimated 130-150 million people (about 2% of the global population) are currently infected with HCV,³³ with an incidence of 3 to 4 million new infections per year.³⁴ Between 70% and 90% of acute HCV infections become chronic and may lead to liver cirrhosis, chronic liver failure, hepatocellular carcinoma, liver transplantation and death.^{7,23,34} Complications of HCV infection are currently the most common indication for liver transplantation. In the United States alone, it is estimated that currently 3 to 4 million people are chronically infected with HCV; it is projected that by the year 2020, about 1 million of those will have cirrhosis.⁶ The risk of hepatic decompensation in subjects with cirrhosis is approximately 5% per year and the 5-year survival rate after decompensation is around 50%.³

HCV has been classified into at least 6 major genotypes (designated 1 to 6) and many subtypes (a, b, c, etc.).⁶ Epidemiology studies have shown marked differences in genotype distribution of HCV by geographic region and patient population. A recent study reported that genotype 1 is estimated to account for more HCV cases globally than any other genotype (46%), followed by genotype 3 (30%), genotype 2 (9%), genotype 4 (8%), genotype 6 (5%), and genotype 5 (<1%).²⁶ Genotype 1b is the most common subtype, accounting for 22% of all infections. Infections in North America, Latin America, and Europe were predominantly genotype 1. North Africa and the Middle East were found to have a large genotype 4 population (71%), which is related to the high prevalence of genotype 4 in Egypt. Asia has predominantly genotype 3 (39%), largely driven by the HCV infections in India and Pakistan, followed by genotype 1 (36%).¹²

1.1.2. Treatment of HCV Infection

Until 2011, standard-of-care treatment for chronic HCV infection consisted of the combination of pegylated interferon (PegIFN) and ribavirin (RBV). In 2011, telaprevir and boceprevir, in combination with PegIFN/RBV, were the first approved direct-acting antivirals (DAAs) for the treatment of chronic HCV infection. SMV and sofosbuvir (SOF) were the first DAAs approved as part of an interferon (IFN)-free regimen for the treatment of chronic HCV infection as specified in their prescribing information.^{27,28,30} Since 2014, additional DAAs, including daclatasvir (DCV; Daklinza⁵), dasabuvir (Exviera⁸) and the fixed-dose combinations SOF/ledipasvir (Harvoni¹³) and ombitasvir/paritaprevir/ritonavir (Viekirax and Technivie^{31,32}), have been approved for use in the United States, European Union and/or in other regions.

The removal of PegIFN and RBV from HCV treatment combinations leads to improved safety and tolerability, with a significant decrease in associated adverse events (AEs). In addition, combinations of DAAs may overcome non-responsiveness to PegIFN by increasing antiviral activity and reducing the risk of developing resistance-associated variants. Furthermore, an all-oral, 1-tablet, fixed-dose-combination treatment without the AEs associated with IFN may facilitate treatment adherence and improve the chance of achieving sustained virologic response (SVR). All-oral treatment regimens consisting of 2 (eg, SMV/SOF; Harvoni, Zepatier, Epclusa, Viekirax/Technivie) or 3 (eg, Viekirax + Exviera/Viekira Pak) DAAs within the classes of HCV NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors have been approved in several countries, and high SVR rates have been demonstrated for such regimens.

New all-oral IFN- and RBV-free regimens are currently under investigation. An optimal IFN-free regimen for treatment of chronic HCV infection requires a combination of agents with different mechanisms of action. Available data suggest that addition of a third anti-HCV agent to a 2-DAA regimen may increase the robustness of the regimen to allow for a shorter treatment duration compared to currently available treatment regimens while maintaining high efficacy, particularly when considering more difficult-to-cure patients.²¹

The current open-label Phase 2b study is designed to investigate efficacy, safety and tolerability, and pharmacokinetics of a once daily (qd) treatment with AL-335, ODV, and SMV for 6 and 8 weeks (3-DAA regimen) in HCV genotype 1, 2, 4, 5 or 6 infected subjects without cirrhosis.

1.1.3. Background of AL-335

AL-335 is a uridine based nucleoside monophosphate prodrug (or nucleotide analog) being developed as an orally administered anti-HCV therapeutic.

A summary of in vitro, nonclinical, and clinical data for AL-335 is provided below; more details can be found in the IB and its addenda.^{16,42,43,}

In Vitro/Nonclinical Data

AL-335 is a potent and highly selective inhibitor of NS5B-directed HCV ribonucleic acid (RNA) replication in vitro, with similar potency across HCV replicons containing NS5B coding sequence derived from genotypes 1a, 1b, 2b, 3a, 4a, 5a and 6a. In a stable HCV genotype 1b replicon, AL-335 demonstrated a 50% effective concentration (EC₅₀) of 0.075 µM. The EC₅₀ of AL-335 against chimeric replicons harboring the NS5B from genotype 2b, 3a, 4a, 5a, and 6a strains was 0.04, 0.06, 0.06, 0.07, and 0.07 µM respectively. AL-335 retains potent antiviral activity against HCV replicons that show resistance to DAAs with other mechanisms of action.

AL-335 (prodrug) is well absorbed in rats and dogs. Both in vitro and in vivo, AL-335 is efficiently and rapidly metabolized to form the active nucleoside 5'-triphosphate (ALS-022235). AL-335 is efficiently converted to ALS-022235 in human hepatocytes. After single oral administration of ¹⁴C-AL-335 to rats and dogs, 15% and 36% of the administered radioactivity was recovered in urine. Oral administration of (non-labelled) AL-335 revealed that AL-335 was recovered mainly as the metabolites in urine with only 0.0006%-0.17% of AL-335 excreted in urine in rats and dogs. In contrast, 0.02%-2% of ALS-022399 (metabolite) and 4%-18% of ALS-022227 (metabolite) is excreted in urine in rats and dogs, respectively.

AL-335 and metabolites (ALS-022399 and ALS-022227; AL-335 and its metabolites ALS-022399 and ALS-22227 are further referred to as AL-335 [and metabolites]) are not expected to cause drug-drug interaction (DDI) with other drugs that are metabolized by cytochrome P450 (CYP) enzymes. AL-335 is metabolized by esterases and is not a substrate of any CYP enzymes. AL-335 (and its metabolites) has demonstrated a very low inhibition potential to CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A. AL-335 is a substrate for P-glycoprotein (P-gp) but does not inhibit P-gp. ALS-022399 and ALS-022227 are neither substrates nor inhibitors of P-gp, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, or organic cation transporter (OCT) 2 transport.

AL-335 was well tolerated in all toxicology studies; following 91 days of repeated dosing, the target organs for toxicity were not identified even when dosed up to the maximum recommended doses of 1,000 mg/kg/day in both rats and dogs. In the dog cardiovascular study, emesis and slight increases in heart rate (~10%) and body temperature (<1°C) were observed at the 1,000 mg/kg dose. All of these findings are monitorable and reversible and all were considered non-adverse.

In vitro inhibition of human deoxyribonucleic acid (DNA) polymerase alpha, beta, and gamma and of human RNA polymerase II was insignificant under the conditions used. In addition, ALS-022235 was not a substrate for the human mitochondrial RNA polymerase and AL-335 did not inhibit mitochondrial protein synthesis in HepG2 cells. Taken together, the data suggest a high degree of selectivity of AL-335 for inhibition of the HCV NS5B polymerase.

Clinical Experience

Up to 28 August 2015, forty (40) healthy volunteers have received single doses up to 1,200 mg (single ascending dose [SAD]) or multiple ascending doses (MAD) of AL-335 of 400 mg and 800 mg for 7 days (AL-335-601). This study also evaluates the monotherapy of AL-335 in HCV genotype 1, 2, 3, and 4-6 infected subjects. In the cohorts completed at the time of the initial protocol writing, subjects had received AL-335 400 mg (genotype 1 only) or 800 mg (genotype 1-4) for 7 days.

In addition, safety data from a DDI study with AL-335, ODV, and SMV (AL-335-602) in healthy subjects are available.

A Phase 2a study (AL-335-604) is ongoing, with AL-335, ODV, and SMV in HCV genotype 1 and 3 infected treatment-naïve subjects. Preliminary data from this ongoing study are available.

More information on the studies including AL-335+ODV±SMV is provided in Section 1.2.

Pharmacokinetics

In the SAD/MAD study (AL-335-601), after single oral ascending doses of 100 to 1,200 mg of AL-335, AL-335 (prodrug) was rapidly absorbed (median time to reach the maximum plasma concentration [t_{max}] 30-45 minutes) and converted to ALS-022399. The terminal elimination half-life ($t_{1/2,term}$) of AL-335 was 30-60 minutes. In healthy volunteers, both the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of AL-335 increased in a dose-proportional manner except at higher doses (ie, 800 and 1,200 mg) for C_{max} which appeared less than dose proportional. Food had a moderate effect on AUC, increasing AL-335 exposure by 61% with no effect on C_{max} . Bioavailability of the oral suspension was lower than the tablets (44% and 42% decrease in C_{max} and AUC, respectively).

Upon multiple dosing up to 800 mg, AL-335 C_{max} and AUC appeared dose proportional between 400 mg and 800 mg; there was no accumulation of AL-335 between Day 1 and 7.

Efficacy and Safety

In the 40 healthy subjects of Study AL-335-601, there were no serious AEs (SAEs), and no clinically relevant laboratory, electrocardiogram (ECG), Holter, vital sign, or physical exam safety signals have been identified. Three subjects reported four AEs, one of which emerged prior to dose administration. For the treatment-emergent AEs, one subject experienced mild intermittent palpitations 72 hours after dosing. The event did not require concomitant medication or other intervention, was not associated with objective evidence of tachycardia, and was deemed unlikely to be related to study drug. The second treatment-emergent AE, moderate dental pain (2 events), occurred 9 hours post-dose and again 6 days after dosing. These events were assessed as unrelated to study drug.

In the same Phase 1b study, multiple ascending doses of AL-335 (400 or 800 mg) over 7 days were evaluated in twenty (20), ten (10), and ten (10) subjects with genotype 1, 2, or 3 chronic

HCV infection, respectively. Thirty-two (32) subjects received active study medication (400 or 800 mg AL-335 [genotype 1], or 800 mg only [genotypes 2 and 3]) and eight (8) received placebo. In Study AL-335-601, monotherapy with AL-335 800 mg qd for 7 days resulted in a mean maximum decline in HCV RNA from baseline of 4.00 log₁₀ IU/mL in HCV genotype 1 and of 4.46 log₁₀ IU/mL and 4.72 log₁₀ IU/mL in HCV genotypes 2 and 3, respectively. In all genotypes tested, HCV RNA returned to baseline levels around 14 days after the last dose (see also Section 1.2).

No SAEs and a total of 26 AEs have been reported after initiation of dosing. The most commonly reported AEs (≥2 events reported) were headache (8 events), increased creatine kinase (CK; 2 events), elevated alanine aminotransferase (ALT; 2 events) and elevated aspartate aminotransferase (AST; 2 events). The ALT and AST elevations each occurred in two subjects ≥10 days after the conclusion of dosing and were similar in magnitude to baseline (pre-dosing) levels. Three AEs occurred one time each: fatigue, common cold, and increased bilirubin. All AEs were mild (8 events) or moderate (8 events) in severity with the exception of one event of elevated CK, which was considered severe but not serious. This subject was asymptomatic and had a history of elevated CK levels related to body building activities. His CK levels peaked at Day 3 of dosing and then declined despite continuing dosing through study completion (Day 7). Including the laboratory-based AEs described above, no clinically relevant laboratory, ECG, Holter, vital sign, or physical exam safety signals have been identified to date.

1.1.4. Background of Odalasvir

ODV is an HCV NS5A inhibitor being developed as an orally administered anti-HCV therapeutic.

A summary of in vitro, nonclinical, and clinical data for ODV is provided below; more details can be found in the Investigator's Brochure (IB) and its addendum.^{15,44}

For details on the IFN-free studies including ODV, see Section 1.2.

In Vitro/Nonclinical Data

ODV is a highly potent HCV NS5A inhibitor with a mean EC₅₀ of 5.3 pM and 26 pM against genotype 1b and 1a HCV replicons, respectively, and 6.4 to 27 pM and 9.0 to 20 pM against chimeric replicons carrying NS5A from genotype 1b and 1a clinical isolates, respectively. The EC₅₀ values of ODV against chimeric replicons carrying the N-terminus of NS5A from representative strains of genotype 2a, 2b, 3a, 4a, 5a, and 6a are 25, 215, 48, 8.0, 15, and 58 pM, respectively. ODV has demonstrated potent antiviral activity against most HCV replicons that show resistance to other HCV NS5A inhibitors.

ODV has a long terminal half-life in plasma (rat: up to 55 hours; dog: up to 114 hours; monkey: 65.8 hours). The t_{1/2} after oral administration was long and was a consequence of slow elimination from tissues and low plasma clearance. A 2- to 5-fold accumulation occurred with multiple dose administration. Plasma protein binding of ODV was 97% or greater in rat, dog, and human plasma.

Preclinical data indicate that 91% to 98% of the administered oral dose of ODV is recovered in excreta by 168 hours post-dose and excretion of drug-derived radioactivity was primarily through biliary and/or gastrointestinal secretion. Drug-derived radioactivity was preferentially distributed into kidneys, brown fat, liver, pancreas, small intestine, thyroid and spleen.

In nonclinical studies, ODV has demonstrated a low inhibition potential for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A. ODV is primarily cleared by biliary secretion, is not significantly metabolized, and is not expected to be involved with clinically significant DDIs associated with the CYP enzyme system. ODV is not an inhibitor of OATP1B1/3, and is neither a substrate nor an inhibitor of transporters such as breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), MRP3, and bile salt export pump (BSEP). ODV is a low-affinity substrate of OATP1B1. ODV is not a substrate but is an inhibitor of P-gp.

The toxicology profile for ODV has been established in single- and repeated-dose toxicology studies, reproductive toxicity studies and genotoxicity studies. ODV was, in general, well tolerated in all toxicology studies.

The heart is a target organ of ODV toxicity based on the findings in repeat-dose toxicity studies in rats and dogs up to 26 weeks duration. While ODV did not have any effect on human ether-a-go-go-related gene (hERG) channel current in vitro or in single-dose cardiovascular safety pharmacology studies in the dog, repeated dosing of ODV in dogs was associated with ECG changes (prolonged PR and/or 1st-degree AV block, prolonged QRS, QT and QTc intervals), and decreased heart rate and echocardiography findings (progressive left ventricular dilatation, eccentric hypertrophy). Increased heart weights were noted following repeated dosing in rats and dogs. All those findings were partially to fully reversible. For more information, see Section 1.3.2.2.

Clinical Experience

As of 9 April 2015, more than 500 healthy volunteers and HCV infected subjects have participated in clinical studies including SAD, MAD, single-dose proof-of-concept, DDI studies, and clinical studies of up to 12 weeks in duration. A total of 440 subjects have received ODV. Of the subjects dosed with ODV, 365 were healthy subjects and 75 were HCV infected subjects. Since 9 April 2015, 2 additional studies, conducted under the responsibility of Alios BioPharma Inc., were initiated, ie, Study AL-335-602 and Study AL-335-604. Pharmacokinetic and safety data from the DDI study AL-335-602 with AL-335, ODV, and SMV in healthy subjects are available. Preliminary data from the ongoing study AL-335-604 with AL-335, ODV, with or without SMV in HCV genotype 1 and 3 infected treatment-naïve subjects are available. More information on these studies including AL-335+ODV±SMV is provided in Section 1.2.

Pharmacokinetics

ODV has a $t_{1/2,term}$ of about 250 hours as determined from single dose data in healthy volunteers. In general, the biphasic decline in plasma concentrations from C_{max} may be characterized by

a rapid phase, followed by a more prolonged, slower phase of decline. In the rapid phase, plasma concentrations generally decline to 10% of C_{max} values by 4-5 days after dose administration. The pharmacokinetic (PK) behavior of ODV is comparable between healthy volunteers and HCV infected subjects. After chronic dosing, the plasma half-life for washout of ODV in HCV infected subjects is approximately 4-5 weeks. Plasma sampling beyond a 12-week dose period suggested that it would take approximately 20-24 weeks after the end of dosing to achieve effective clearance of the drug.

No clinically significant DDI was observed between ODV and sovalprevir, montelukast, atazanavir/ritonavir, efavirenz/emtricitabine/tenofovir disoproxil fumarate, darunavir/ritonavir, or raltegravir.

Efficacy and Safety

Efficacy data on different DAA combinations including ODV are described in Section 1.2.

In the completed clinical studies of ODV, including administration of single ODV doses as high as 1,000 mg, and multiple qd doses as high as 100 mg for 14 days in healthy volunteers, and 75 mg for 12 weeks in chronic HCV infected subjects, ODV has been well tolerated. In some studies, the ODV dose regimens included a loading dose on Day 1, but ODV in combination with SOF has been used successfully without a loading dose in a recent Phase 2a study, ACH102-017. ODV has been studied in combination with other anti-viral agents such as RBV, sovalprevir, and SOF, and has been well-tolerated in each of these settings as well.

Cardiac monitoring in these studies with ODV in HCV infected subjects did not identify any clinically significant trends. One SAE of asymptomatic second-degree Mobitz type 1 atrioventricular (AV) block was reported in a subject in Study AL-335-604 with a borderline elevated PR interval at screening. The event led to discontinuation of the study drugs (AL-335, ODV, and SMV) and was considered probably related to ODV by the investigator. Echocardiography remained normal and the event was considered a benign conduction disorder which appeared to have settled 4 days after study drug discontinuation, and no further investigations were considered needed. In Study ACH102-005 a treatment-emergent PR prolongation was observed; this event evolved to a transient type 1 second-degree atrioventricular (AV) block. The cardiologist assessed the subject's second-degree AV block to be of undetermined etiology but unlikely due to study drug. The subject completed the full course of 12 weeks therapy with ODV and RBV. Based on the currently available data the cardiac safety profile of ODV is acceptable to conduct the present study.

1.1.5. Background of Simeprevir

SMV is an HCV NS3/4A protease inhibitor approved in 2013 in the United States, Canada, and Japan for the treatment of patients with chronic HCV genotype 1 infection. Since that time, SMV has been approved in the European Union and multiple other countries and regions globally for the treatment of chronic HCV genotype 1 and 4 infection with and without human immunodeficiency virus (HIV) co-infection. Additional registration procedures are ongoing worldwide. The marketed SMV formulation is an oral capsule. Each hard capsule contains SMV

sodium equivalent to 150 mg (globally except Japan) or 100 mg (Japan only). The estimated cumulative post-authorization exposure to SMV is over 95,000 treatment courses (from launch to 31 May 2015).

A summary of in vitro nonclinical and clinical data for SMV relevant to the present study is provided below; more details can be found in the IB and its addendum.^{17,18} For details on IFN-free studies including SMV, see Section 1.2.

In vitro/Nonclinical Data

SMV is highly protein-bound in plasma (>99.9%) at pharmacologically relevant concentrations.

The median SMV EC₅₀ and EC₉₀ values against an HCV genotype 1b replicon were 9.4 nM (7.05 ng/mL) and 19 nM (14.25 ng/mL), respectively. Chimeric replicons carrying NS3 sequences derived from HCV protease inhibitor treatment-naïve genotype 1a and genotype 1b patients displayed median fold change (FC) in EC₅₀ values of 1.4 (N=78) and 0.4 (N=59) compared to reference genotype 1b replicon, respectively. Genotype 1a and 1b isolates with a baseline Q80K polymorphism resulted in median FC in SMV EC₅₀ of 11 (N=33) and 8.4 (N=2), respectively. Median SMV FC values against genotype 2 and genotype 3 baseline isolates tested were 25 (N=4) and 1,014 (N=2). Median SMV FC values against genotype 4a, 4d, and 4other baseline isolates tested were 0.5 (N=38), 0.4 (N=24), and 0.8 (N=29), respectively.

Clinical Experience

Clinical data for SMV in combination with RBV/PegIFN are available from 9 global Phase 3, 2 Phase 2b and 2 Phase 2a clinical studies. During these studies 2,649 HCV infected subjects were exposed to SMV. Of these, 1,808 HCV infected subjects were treated with SMV 150 mg qd for 12 weeks. Data from SMV IFN-free clinical studies are available from 2 Phase 3 and 2 Phase 2 studies. In these studies, 580 HCV infected subjects received SMV in combination with SOF with or without RBV and 168 HCV infected subjects received SMV in combination with DCV with or without RBV. Other SMV-containing IFN-free studies are ongoing. In addition, data are available from 30 Phase 1 studies, during which 1,027 non-HCV infected subjects were exposed to SMV and 8 studies conducted in Japan (4 Phase 3, 1 Phase 2 and 2 Phase 1 studies) including 434 HCV infected treatment-naïve and treatment-experienced subjects who received SMV.

Pharmacokinetics

The blood:plasma ratio of SMV is approximately 0.66, indicating that SMV is largely contained in the plasma rather than the cellular components of the blood.

SMV formulated as an oral capsule, was readily absorbed. In healthy subjects, t_{max} was 4 to 6 hours.

In chronic HCV genotype 1 infected subjects, the exposure was generally greater than observed in healthy subjects. In subjects with chronic hepatitis C, t_{1/2,term} was approximately 41 hours,

a profile that supports a qd dosing regimen. Renal clearance plays an insignificant role in the elimination of SMV and its metabolites.

Compared to intake without food, administration of SMV with food to healthy subjects increased the AUC by 61% after a high-fat, high-caloric breakfast (928 kcal) and by 69% after a normal-caloric breakfast (533 kcal), and delayed the absorption by 1 hour and 1.5 hours, respectively. SMV should be taken with food.

A number of Phase 1 PK and DDI studies have been conducted with SMV and are summarized in the IB including the following: the methadone interaction study C110 that demonstrated no interaction between SMV and methadone.

CYP3A enzymes are mainly involved in the metabolism of SMV.

SMV is a mild inhibitor of intestinal (but not hepatic) CYP3A activity and a mild inhibitor of CYP1A2. In addition, DDI studies with transporter substrates suggest that SMV likely inhibits P-gp and OATP1B1 in vivo.

Efficacy and Safety

SMV at a dose of 150 mg qd in combination with PegIFN/RBV has demonstrated statistically significantly higher efficacy compared to PegIFN/RBV alone and a favorable safety/tolerability profile in HCV treatment-naïve and -experienced subjects with chronic HCV genotype 1 with or without HIV-1 co-infection and in subjects with chronic HCV genotype 4 infection, with no clinically relevant additional toxicity.^{27,28}

SVR rates of SMV in combination with PegIFN/RBV were reduced in subjects with hepatitis C genotype 1a with NS3 Q80K polymorphism compared to subjects without Q80K polymorphism.

In the Phase 2a study C202, treatment-naïve subjects with HCV genotypes 2, 3, 4, 5, and 6 infection were treated with SMV 200 mg qd monotherapy for 7 days. Monotherapy with oral SMV 200 mg qd for 7 days showed potent antiviral activity against HCV genotype 2, 4, 5, and 6. For the primary endpoint at Day 8, the mean (\pm SE) change in plasma HCV RNA (\log_{10} IU/mL) from baseline was the greatest for genotypes 6 (-4.35 ± 0.29) and 4 (-3.52 ± 0.43), followed by genotypes 2 (-2.73 ± 0.71) and 5 (-2.19 ± 0.39). No clear antiviral activity with SMV monotherapy was observed against HCV genotype 3. The efficacy in HCV genotype 4 infected subjects was confirmed in the Phase 3 study HPC3011.

In Phase 2 study HPC2002 and Phase 3 studies HPC3017 and HPC3018, high SVR12 rates were observed in HCV infected subjects treated with SMV and SOF; for more details, refer to Section 1.2.

1.2. Background to All-oral Combination Regimens

A summary of available data for AL-335, ODV, and SMV containing all-oral regimens in HCV infected subjects is provided below.

NS3/4A Protease Inhibitor and Nucleotide NS5B Polymerase Inhibitor (SMV/SOF)

In a Phase 2 study (HPC2002) in HCV genotype 1 infected treatment-naïve subjects and null responders to prior PegIFN/RBV therapy who were treated with **SMV** 150 mg qd for 12 or 24 weeks in combination with **SOF** 400 mg qd with or without RBV, high SVR 12 weeks after the end of treatment (SVR12) rates ($\geq 90\%$) were observed irrespective of treatment duration, treatment with or without RBV, and prior treatment history. The overall SVR12 rate in subjects receiving 12 weeks of SMV in combination with SOF with or without RBV was 94%. Similar SVR12 rates were observed for HCV genotype 1a infected subjects with and without baseline Q80K polymorphism.

In Phase 3 studies HPC3017 and HPC3018 treatment-naïve and treatment-experienced (to prior IFN-based treatment with or without RBV) subjects with chronic HCV genotype 1 infection, without and with cirrhosis, respectively, were treated with SMV 150 mg qd in combination with SOF 400 mg qd for 12 or 8 weeks.

- For chronic HCV genotype 1 infected subjects **without cirrhosis** who were HCV treatment-naïve or treatment-experienced superiority of the 12-week treatment regimen of SMV+SOF to a historical control (ie, composite of approved DAA/PegIFN/RBV regimens) was concluded based on the primary analysis of study HPC3017. The SVR12 rate of the 12-week treatment regimen was 96.8% versus 87% for the historical control. High SVR12 rates were observed for the 12-week regimen, regardless of the subgroup analyzed.

The 8-week SMV+SOF regimen in study HPC3017 was not superior to a historical control. The SVR12 rate of the 8-week regimen was 82.6% versus 83% for the historical control. Higher SVR12 rates were observed among those subjects with more favorable demographic and baseline disease characteristics.

- For chronic HCV genotype 1 infected subjects **with cirrhosis** who were HCV treatment-naïve or treatment-experienced superiority of the 12-week treatment regimen of SMV+SOF to a historical control was concluded based on the primary analysis of study HPC3018. The SVR12 rate of the 12-week treatment regimen in study HPC3018 was 83.5% versus 70% for the historical control.

Pooled data from HPC2002, HPC3017, and HPC3018 indicated that treatment of HCV genotype 1 infected subjects who are treatment-experienced or treatment-naïve (with or without cirrhosis) with SMV 150 mg qd and SOF 400 mg qd was generally safe and well tolerated irrespective of the treatment duration (8, 12, or 24 weeks of SMV+SOF). No new confirmed safety issues were identified other than those observed with SMV in combination with PegIFN and RBV.

Serious AEs and AEs leading to discontinuation of study drugs were rare in these studies.

Although there was a trend for a higher incidence of AEs in subjects receiving 24 weeks of treatment, no clinically relevant differences were observed in the incidence of grade 3 or 4 AEs, SAEs, or AEs leading to discontinuation of study drugs between the 8-, 12-, and 24-week treatment duration group. No clinically relevant differences in safety were observed between the subgroup of patients with cirrhosis as compared to those without cirrhosis despite a trend towards more rash AEs of clinical interest in cirrhotic subjects.

NS3/4A Protease Inhibitor and NS5A Inhibitor (SMV/DCV, ODV/sovaprevir)

The AI444-062 Phase 2 study, performed by Bristol-Myers Squibb, evaluated the use of **SMV** 150 mg qd in combination with **DCV** 30 mg qd, with and without RBV, for 12 or 24 weeks in subjects with chronic HCV genotype 1 infection who were HCV treatment-naïve (N=116) or null responders to prior PegIFN/RBV therapy (N=52).³⁵ SVR12 was achieved in 74.5% and 84.9% of HCV genotype 1b infected treatment-naïve subjects treated with and without RBV, respectively, and in 65.2% and 95.0% of HCV genotype 1b infected prior null responders treated without and with RBV, respectively. Subjects with genotype 1a infection all received SMV and DCV with RBV and SVR12 rates for treatment-naïve subjects were 66.7%; viral breakthrough occurred frequently in the prior null responders (7 of 9 subjects).

Treatment with SMV 150 mg qd and DCV 30 mg qd with or without RBV was generally safe and well tolerated. Most AEs were grade 1 or 2. Grade 3 or 4 AEs were reported in 10% (9/92) and 5% (4/76) of subjects treated with SMV and DCV with and without RBV, respectively. One death during treatment was reported (trauma-associated intracranial hematoma, unrelated to study drug). SAEs occurred in 4% (4/92) and 9% (7/76) of subjects treated with SMV and DCV with and without RBV, respectively. SAEs were related to study drug in 2 subjects (neurotoxicity, liver disorder). AEs leading to early discontinuation were reported in 2% (2/92) and 3% (2/76) of subjects treated with SMV and DCV with and without RBV, respectively. Three subjects had treatment-related AEs leading to early discontinuation (constipation, neurotoxicity, insomnia/sleep terror). Grade 3 or 4 hyperbilirubinemia occurred in 15% (14/92) and 4% (3/76) of subjects treated with SMV and DCV with and without RBV, respectively.

ACH102-007 was a placebo-controlled Phase 2 study to evaluate the safety, tolerability, and efficacy of **ODV** and **sovaprevir** in combination with RBV for 12 weeks in chronic HCV genotype 1 infected subjects. A total of 30 subjects were enrolled, of whom 20 received active treatment, and 10 received placebo. For active subjects, the ODV dosing regimen was a 150 mg loading dose on Day 1, followed by a 50 mg daily dose for the remainder of the treatment duration; sovalprevir was administered as either a 200 mg (Group 1) or 400 mg (Group 2) daily dose; and RBV dosing was weight-based as per the label. All doses were to be taken with food. For both Group 1 and Group 2, administration of sovalprevir, ODV, and RBV was associated with rapid and sustained reductions in HCV RNA, while placebo subjects had little or no change in viral load. Viral clearance occurred by Week 2 in all active subjects who received at least two weeks of study drugs. There have been three viral breakthroughs in Groups 1 and 2 each, all occurring in subjects with the genotype 1a HCV subtype. In contrast, no subjects with HCV genotype 1b infection have had viral breakthrough or relapse to date. Both combination dosing regimens were well tolerated with no drug-related SAEs and no discontinuations for safety.

Trough concentrations of ODV concentrations were similar in Group 1 (200 mg sovalprevir) and Group 2 (400 mg sovalprevir), suggesting no effect of sovalprevir dose on ODV concentrations.

Nucleotide NS5B Polymerase Inhibitor and NS5A Inhibitor (ODV/SOF)^{1,15}

ACH102-017 is a Phase 2 study to evaluate the safety, tolerability, and efficacy of **ODV** in combination with **SOF** (a nucleotide analog HCV inhibitor) for 6 or 8 weeks in chronic HCV genotype 1 infected subjects. The dosing regimen was 50 mg liquid-filled capsule formulation of ODV given in the fasted condition without a loading dose plus 400 mg of SOF for either 8 weeks (Group 1; N=18, ie, 12 on active treatment and 6 observational subjects) or 6 weeks (Group 2; N=12, the 6 observational subjects from Group 1 + 6 additional subjects). Preliminary PK results suggest that ODV and SOF concentrations in this study are similar to those expected based on historical data. Group 1 included 10 subjects with HCV genotype 1a; median HCV RNA in Group 1 was 7.15 log₁₀ IU/mL (range: 5.5-7.8 log₁₀ IU/mL). Group 2 included 6 subjects with HCV genotype 1a; median HCV RNA at baseline in Group 2 was 6.95 log₁₀ IU/mL (range: 6.2-8.0 log₁₀ IU/mL). All 12 (100%) subjects in Group 1 and all 12 (100%) subjects in Group 2 achieved SVR24. Six additional rollover subjects (Group 3) also received 6 weeks of treatment consisting of ODV 50 mg + SOF 400 mg qd. Five out of the 6 were HCV genotype 1a infected subjects, 4/6 had interleukin-28B (*IL28B*) genotype non-CC (2 subjects with *IL28B* genotype TT) and median baseline HCV RNA was 6.32 log₁₀ IU/mL (range: 6.0-7.3 log₁₀ IU/mL). All 6 (100%) subjects achieved SVR12.

The dosing regimen was well tolerated in both groups with no SAEs or discontinuations for safety. No significant ECG findings or lab abnormalities were observed during treatment.

3-DAA Combination (SMV/DCV/SOF, SMV/ODV/AL-335)

At the time of the initial protocol writing, interim results from the Phase 2 IMPACT (HPC2010) study, investigating SMV 150 mg qd + DCV 60 mg qd + SOF 400 mg qd for 12 weeks in treatment-naïve and treatment-experienced subjects with chronic HCV genotype 1 or 4 infection and decompensated liver disease were available. The combination of SMV/DCV/SOF resulted in high on-treatment virologic response and 100% SVR12 rates in HCV genotype 1 or 4 infected subjects with compensated liver disease. All subjects (100%) with available data in both the Child-Pugh A (N=19) with evidence of portal hypertension and Child-Pugh B (N=9) groups achieved SVR4. SMV exposures in Child-Pugh B subjects were within the range observed for Child-Pugh A. The combination was generally safe and well tolerated; AEs were grade 1 or grade 2 in severity with no AE-related treatment discontinuations.

Since the writing of the initial protocol, a DDI study, AL-335-602, involving 32 subjects over 2 groups, evaluating varying combinations of daily dosing over 23 days with AL-335 (800 mg), ODV (150 mg loading dose followed by 50 mg maintenance doses), and SMV (150 mg) was completed. Pharmacokinetic data indicated that AL-335 had no impact on either SMV or ODV exposures (AUC). ODV increased SMV exposures (AUC_{0-24h}) by approximately 1.8-fold. SMV increased ODV exposure (AUC_{0-24h}) by 1.5-fold. Co-administration of all 3 drugs resulted in significant increase in AL-335 (prodrug) exposures (6.9- to 8.2-fold) and metabolite ALS-022399 (2.6- to 2.8-fold), with no effect on metabolite ALS-022227 (1- to 1.1-fold)

In study AL-335-602, repeated daily administration of oral ODV (150 mg loading dose followed by 50 mg maintenance doses) as monotherapy or as combination with AL-335 (800 mg) and/or SMV (150 mg) for 23 days, was well tolerated in this study. All treatment emergent AEs (N=20) were assessed as mild (N=14) or moderate (N=6; oropharyngeal pain, tooth abscess, alkaline aminotransferase [ALT] increase, and fatigue [3 events]), in severity by the investigator. The most commonly reported treatment emergent AEs (≥ 2 events) were fatigue (8 events) and diarrhea/soft feces (3 events), neither of which was considered clinically concerning or suggestive of a safety signal which would preclude dosing with any combination of the study drugs. No SAEs and no medically significant events were reported. One adverse event (AE), tooth abscess, led a subject to prematurely discontinue study drugs. One subject experienced increased ALT (grade 3)/AST (grade 2) levels which were attributed to new onset cytomegalovirus infection. The increased ALT/AST values returned to within the normal range by the end of the study. With the exception of the subject with increased ALT/AST, no clinically significant abnormalities with respect to laboratories, vital signs, physical examinations, or ECGs were identified. A Phase 2a, open-label study (AL-335-604) to evaluate the safety, PK, and efficacy of the combination of AL-335+ODV \pm SMV in HCV genotype 1 and 3 infected treatment-naïve subjects has been initiated under the responsibility of Alios BioPharma Inc. Preliminary data from 7 cohorts are available from an analysis with cut-off date 22 June 2016 which is based on a snapshot database (no official database lock and cleaning was performed). Additional preliminary key HCV RNA and safety data obtained since 22 June through 3 August 2016 are provided below. Subjects in Cohorts 1, 1b, 2, 3, and 4 were infected with HCV genotype 1 and had no cirrhosis. Subjects enrolled in Cohort 5 were infected with HCV genotype 3 without cirrhosis and subjects enrolled in Cohort 6 were infected with HCV genotype 1 and had Child-Pugh A cirrhosis.

In Cohort 1 (AL-335 400 mg qd, ODV 50 mg qd, and SMV 100 mg qd for 8 weeks), Cohort 2 (AL-335 800 mg qd, ODV 50 mg qod, and SMV 75 mg qd for 8 weeks) and Cohort 3 (AL-335 800 mg qd, ODV 50 mg qod, and SMV 75 mg qd for 6 weeks), all subjects received the 3-DAA regimen. As of 22 June 2016, in Cohort 1 all subjects (20/20) had HCV RNA not detected or <lower limit of quantification (LLOQ) at the follow-up Week 12 and follow-up Week 24 time points (100% SVR12 and 100% SVR24). All subjects in Cohort 2 (20/20) had HCV RNA not detected or <LLOQ at the follow-up Week 12 time point (100% SVR12; SVR24 data not yet available). In Cohort 3 all subjects (20/20) had HCV RNA not detected or <LLOQ at the follow-up Week 4 time point (100% SVR4) and all 14 patients with data available from the follow-up Week 8 visit had HCV RNA not detected or <LLOQ at this time point (100% SVR8, SVR12 data not yet available).

No subjects in Cohort 5 (HCV genotype 3 infected subjects treated with AL-335 800 mg qd, ODV 50 mg qod, and SMV 75 mg qd for 8 weeks) or Cohort 6 (HCV genotype 1 infected subjects with compensated cirrhosis treated with AL-335 800 mg qd, ODV 50 mg qod, and SMV 75 mg qd for 8 weeks) have completed dosing. No cases of viral breakthrough or viral relapse are known to have occurred in any cohorts including 3-DAA treatment as of the 3 August 2016 data cut-off.

In Cohort 1b, HCV genotype 1 infected subjects without cirrhosis received the 2-DAA regimen of AL-335 and ODV (AL-335 800 mg qd + ODV 50 mg qod without SMV for 8 weeks). In this cohort, at the SVR12 visit, 18/20 (90%) subjects had HCV RNA not detected or <LLOQ. Two subjects (10%) experienced viral relapse between the follow-up Week 8 and follow-up Week 12 visit and follow-up Week 4 and follow-up Week 12 assessments (follow-up Week 8 visit was not completed), respectively. No ODV or AL-335 resistance-associated variants (RAVs) were observed at baseline in the 2 subjects with viral relapse, both infected with HCV genotype 1a. At time of viral relapse both subjects had emerging ODV RAVs at NS5A amino acid positions 28 or 93 (M28T in combination with T64A in 1 subject; Y93H in combination with T21A in the other subject) and no emerging AL-335 RAVs. Of the 5 subjects in Cohort 4 (AL-335 800 mg qd + ODV 50 mg qod without SMV for 8 weeks) that have completed treatment and reached the follow-up Week 4 visit as of the 3 August 2016 cut-off, 1 further subject infected with HCV genotype 1a is known to have experienced viral relapse. This viral relapse was identified on 2 August 2016 and viral sequencing is pending. No other cases of viral relapse or viral breakthrough are known to have occurred in any cohorts including 2-DAA treatment as of the 3 August 2016 data cut-off.

Taken together, the available safety data from Study AL-335-604 up to 22 June 2016 indicate that dosing with AL-335 in combination with ODV±SMV at several dose combinations is generally safe and well tolerated. No clear safety signals have been identified in terms of treatment-emergent AEs, laboratory abnormalities, ECGs and echocardiograms.

In this study, up to 22 June 2016, 97 subjects received at least 1 dose of study medication. Overall (Cohorts 1, 1b, 2, 3, 4, 5 and 6 combined), as of 22 June 2016, 173 treatment-emergent AEs have been reported. All treatment-emergent AEs were mild (N=162 events) or moderate (N=11 events) in severity; no severe or life-threatening AEs were reported. The most commonly reported treatment-emergent AEs (≥5% of the subjects) are headache (17 subjects; 17.5%), fatigue (13 subjects; 13.4%), upper respiratory tract infection (10 subjects, 10.3%), contusion (8 subjects 8.2%), insomnia (6 subjects; 6.2%) and diarrhea, cough and accidental overdose of study medication (5 subjects each; 5.2%). The reported overdoses generally involved subjects who took ODV qd instead of qod (Cohorts 1b-3) or misunderstood dosing instructions or both. None of these overdose events involved ingestion of clinically important excesses of study drug, none were associated with any symptomatology, and none were intentional. All subjects that experienced these overdoses were re-educated about dosing instructions and subsequently completed their treatment course. None of the reported treatment-emergent AEs are considered suggestive of a safety signal.

Two treatment-emergent SAEs were reported in the study. One event occurred in a subject in Cohort 1b who was diagnosed with a transitional cell carcinoma of the urethra. This event was identified during treatment when the subject was worked up for an approximately 5-month history of recurrent urinary tract infections and macroscopic hematuria. This disease was likely present at baseline, but unrecognized, and was considered unrelated to study drug by the investigator. The other treatment-emergent SAE occurred in a subject in Cohort 1 who experienced a progressive increase in PR interval from baseline to Mobitz Type I 2nd degree

atrioventricular (AV) block (Wenckebach, toxicity grade 2) at Week 5 of treatment. More information on this SAE is provided in Section 1.3.2.2.

Two subjects prematurely discontinued 1 or more study drugs. The first subject discontinued all 3 study drugs after experiencing Mobitz Type I 2nd degree AV block (SAE) described above. The second subject had an elevated PR interval (mean: 234 milliseconds) at baseline which did not change significantly post-baseline (maximum mean: 257 milliseconds). This was not considered a treatment-emergent AE, however, in light of the second degree AV block described above, ODV was discontinued in this subject as a precaution at treatment Week 5. The subject continued AL-335 and SMV through Week 8.

Between 22 June and 3 August 2016, no additional treatment-emergent SAEs, serious/life threatening treatment-emergent AEs, or treatment-emergent AEs leading to study drug discontinuation were reported in this study.

No subjects had grade 3 or 4 hematology laboratory abnormalities and there were no grade 3 or 4 urinalysis abnormalities.

Several subjects experienced treatment-emergent chemistry laboratory abnormalities of grade ≥ 3 ; grade 3 elevation of creatine kinase in 1 subject, grade 3 increase in cholesterol in 1 subject, and 3 subjects experienced grade 3 (2 subjects) or grade 4 (1 subject) lipase levels. None of the abnormalities were considered clinically significant by the investigator or resulted in premature discontinuation of the study drugs.

Apart from the subject in Cohort 1 who was identified as developing 2nd degree AV block type Wenckebach, which resulted in study drug discontinuation, no other post-baseline ECGs were considered to have an overall interpretation which is clinically concerning or suggestive of a safety signal.

No echocardiogram was interpreted by the central reader to be clinically significantly abnormal and no echocardiogram finding was associated with symptoms or resulted in study drug discontinuation.

The doses of the study drugs in the current study were selected based on review of the on-treatment responses and the evaluation of the safety and PK data from Phase 1 and Phase 2a studies.

1.3. Risk Benefit Section

1.3.1. Known Benefits and Risks

Known Benefits and Risks for AL-335

Please see Section [1.1.3](#).

AL-335 is a potent and highly selective inhibitor of NS5B-directed HCV RNA replication in vitro, including replication of replicons containing NS5B sequences derived from isolates of genotypes 1a, 1b, 2b, 3a, 4a, 5a and 6a.

A formal Adverse Drug Reaction (ADR) analysis has not yet been conducted for AL-335.

Known Benefits and Risks for ODV

Please see Section [1.1.4](#) and Section [1.2](#).

ODV is an inhibitor of the HCV NS5A protein with potent in vitro activity against genotype 1 replicons and against chimeric replicons containing the N-terminus of NS5A of genotypes 2-6. For the majority of mutations associated with resistance to first generation NS5A inhibitors the effect on the in vitro activity of ODV is substantially lower than for first generation NS5A inhibitors, in particular in genotype 1b. In a proof-of-concept study in HCV genotype 1 infected subjects, ODV has shown potent antiviral activity after a single dose for all dose groups tested.

In a Phase 2a study (ACH102-017), ODV in a 2-DAA combination with SOF with a treatment duration of 6 weeks has shown an efficacy of 100% SVR in treatment-naïve HCV genotype 1 infected subjects without cirrhosis.

In a placebo-controlled Phase 2 study in HCV genotype 1 infected subjects, administration of sovalprevir (an HCV NS3 inhibitor), ODV, and RBV for short durations of 12 weeks in treatment-naïve genotype 1 HCV infected subjects was associated with rapid reductions in HCV RNA but the viral failure rate was high in patients with genotype 1a.

A formal ADR analysis has not yet been conducted for ODV. However, an internal assessment of all pre-clinical and clinical information available at the time of the protocol writing has identified the effect of ODV on cardiac conduction as a potential risk. Details are discussed in Section [1.3.2](#).

Known Benefits and Risks for SMV

Please see Section [1.1.5](#) and Section [1.2](#).

SMV is an inhibitor of the HCV NS3/4A protease which is essential for viral replication. In a biochemical assay, SMV inhibited the proteolytic activity of recombinant genotype 1a and 1b HCV NS3/4A proteases, with median kinetic inhibition constant values of 0.5 nM and 1.4 nM, respectively.

In HCV genotype 1 treatment-naïve and treatment-experienced subjects, SMV 150 mg qd administered for 12 weeks with PegIFN α -2a/RBV or PegIFN α -2b/RBV for response-guided 24 or 48 weeks was superior (based on the primary endpoint, SVR12) to placebo with PegIFN/RBV alone for 48 weeks. SMV in combination with PegIFN/RBV has also been shown to be efficacious in HCV genotype 4 and HIV/HCV genotype 1 infected subjects.

SMV at a dose of 100 mg qd in combination with PegIFN/RBV has demonstrated good efficacy and a favorable safety/tolerability profile in Japanese and Caucasian HCV genotype 1 treatment-naïve and treatment-experienced subjects.

HPC3005, a Phase 3 study which included treatment-naïve chronic HCV genotype 1 infected Asian subjects from China and South Korea, demonstrated superiority of both SMV 100 mg ($p=0.003$) and SMV150 mg ($p\leq 0.001$) both for 12 weeks in combination with response-guided PegIFN/RBV (24 or 48 weeks) over PegIFN/RBV for 48 weeks in terms of SVR12 (88.9% in the SMV 100 mg arm, 90.8% in the SMV 150 mg arm and 75.7% in the placebo arm).

The observed safety profile of SMV150/PegIFN/RBV in Asian subjects from China and South Korea was similar to the known safety profile of SMV 150 mg in Caucasian subjects despite the 2.1-fold higher exposure (mean AUC from time 0 to 24 hours after dosing [AUC_{24h}]). The overall incidence of AEs was similar in all the treatment arms, with no relevant differences in the safety profile of the SMV arms, except for events of increased bilirubin. The majority of these events were grade 1 or 2, in general not associated with increases in liver transaminases, and reversible on completion of SMV/placebo.

SMV 150 mg qd in combination with SOF 400 mg qd for 12 weeks in HCV genotype 1 infected subjects without cirrhosis achieved high SVR12 (>92%) irrespective of baseline characteristics and was safe and well tolerated. SMV 150 mg qd in combination with SOF 400 mg qd for 12 weeks in HCV genotype 1 infected subjects with cirrhosis achieved SVR12 rates of 83.5%. Although superiority of the SMV+SOF treatment over a composite historical control^a could be concluded (95% confidence interval [CI]: 75.8%-91.1%; lower limit of the 95% CI was higher than the SVR12 historical control rate [70%]), it is recommended that patients HCV genotype 1 infected patients are treated with SMV/SOF for 24 weeks.

SVR rates of SMV in combination with PegIFN/RBV were reduced in subjects with HCV genotype 1a with NS3 Q80K polymorphism compared to subjects without Q80K polymorphism. In HCV genotype 1a infected subjects without cirrhosis, efficacy of SMV in combination with SOF at the recommended 12-week treatment duration was not impacted by the presence of NS3 Q80K polymorphism.

^a The SVR12 historical control considered the most appropriate was a composite of the historical SVR12 rates of approved DAA/PegIFN/RBV-based regimens (ie, the best SVR of any approved regimen at the time of study conception) in the subpopulations depending on the proportion of treatment-naïve, prior relapser, prior nonresponder, IFN-intolerant, and “other” subjects enrolled in this study. This was the best SVR rate of an approved regimen at the time of study conception (ie, SMV or SOF + PegIFN/RBV) in the subpopulations with data available.

Adverse reactions of SMV: SMV 150 mg qd was generally safe and well tolerated when administered for a duration of 12 weeks in combination with PegIFN/RBV to adults with compensated liver disease with or without HIV co-infection.

The grouped terms identified as SMV adverse reactions are constipation, blood bilirubin increased, photosensitivity reaction, pruritus, and rash.

In the pooled data set from the three placebo-controlled Phase 3 studies (C208, C216, and HPC3007) of SMV in combination with PegIFN/RBV, at least one SMV adverse reaction was reported in 44.7% of SMV-treated subjects and in 31.2% of subjects on placebo, during the first 12-week phase. Adverse reactions reported in SMV-treated subjects and subjects on placebo were pruritus (21.9% vs 14.6%), rash (21.8% vs 16.6%), blood bilirubin increased (7.4% vs 2.8%), photosensitivity reaction (4.7% vs 0.8%), and constipation (2.6% vs 2.5%). With exception of constipation, incidences were higher in the SMV-treated subjects, but the differences between the treatment groups became smaller when considering the entire treatment phase. For constipation, the time to onset was shorter in the SMV group than in the placebo group.

Most adverse reactions were grade 1 or 2 in severity. During the first 12 weeks of treatment (SMV + PegIFN/RBV), the incidence of grade 3 or 4 adverse reactions (2.8% in SMV-treated subjects and 0.5% [2 subjects] in subjects on placebo), serious adverse reactions (0.3% [2 subjects] vs 0.0% [none]), and adverse reactions leading to SMV/placebo discontinuation (0.9% [7 subjects] vs 0.3% [1 subject]) was low.

No safety issues other than the known adverse reactions could be identified in Japanese subjects or Asian subjects from China and South Korea.

A formal adverse reaction identification process was conducted on the pooled clinical safety data of HPC2002, HPC3017, and HPC3018 (SMV+SOF). No new adverse reactions of SMV could be identified.

In total, during the treatment phase, adverse reactions were reported in 19.9% of the subjects. The majority of the adverse reactions were grade 1 or 2 in severity. The overall incidence of adverse reactions was similar for all studied treatment durations (8, 12, or 24 weeks), except for events of rash (grouped term), for which there was a slight trend towards a higher proportion of subjects with events in the 24-week treatment group than in the 8-week or the 12-week treatment group (4.5% of subjects in the 8-week treatment group, 8.0% of subjects in the 12-week treatment group, and 12.9% in the 24-week treatment group). Most rash events were grade 1 or 2 in severity and 1 case, reported in the 12-week treatment group, led to discontinuation of study drugs, as mandated by the protocol.

None of the above-mentioned adverse reactions require monitoring beyond the guidance per the product information of the co-administered HCV medication, if applicable. As specified in the SMV product information, patients must use appropriate sun protective measures during treatment with SMV. Excess exposure to sun and use of tanning devices during treatment with SMV should be avoided (see Section 4.3).

1.3.2. Potential Benefits and Risks

1.3.2.1. Potential Benefits

For the subjects in this study, the status of their HCV infection and general health will be closely monitored. It is possible that by participating in this study the subject's general health and HCV disease status will improve. The use of a 3-DAA combination in this study (including agents with a high genetic barrier) may increase the robustness of the regimen allowing for shorter treatment durations compared to currently available treatment regimens to achieve cure for all infected patients irrespective of genotypes or any other baseline factor, all without compromising patient compliance and safety.

1.3.2.2. Potential Risks

Every medication can have **undesirable effects**.

Potential Risks for AL-335

- **Nonclinical Safety Evaluations:**

The toxicology profile for AL-335 has been established in multiple in vitro and in vivo studies. AL-335 was well tolerated in all toxicology studies; following 14 days of repeated dosing, the target organs for toxicity were not identified even when dosed up to the maximum recommended doses of 1,000 mg/kg/day in both rats and dogs.

Because nucleosides, as a class, have a known risk of mitochondrial toxicity, which is often manifested as muscle injury, this study will systematically assess study subjects for laboratory abnormalities which might be present after muscle injury. Specifically, CK is checked throughout the study treatment period. The potential risk of developing any of these abnormalities is considered to be very low as AL-335 did not exhibit mitochondrial toxicity in in vitro or in vivo toxicology studies. In addition, a toxicity management plan for mitochondrial toxicity is included in the protocol (see Section 9.8.6.6).

Potential Risks for ODV

The heart is a target organ of ODV toxicity based on the findings in repeat-dose toxicity studies in rats and dogs up to 26 weeks duration. In vitro, ODV has shown to have no effect on hERG channel currents at the maximal feasible concentration (5 µM) tested which was at least 500 times the target clinical mean plasma concentration of unbound ODV, indicating a large safety margin with regards to QT prolongation. Odalasvir also did not have any effect in single-dose dog cardiovascular safety pharmacology studies. Additional information about a potential QT effect in humans will be collected in a planned modified thorough QT study.

Summary of cardiac safety in animal studies

In vivo, no cardiac effects occurred at exposure levels (C_{max} and AUC) about 6 times the target clinical exposure of ODV (when administered at a dose of 25 mg qd in combination with SMV 75 mg qd and AL-335 800 mg qd).

After repeated dosing of ODV in rats and dogs with exposure levels (C_{max} and AUC) 14 times the target clinical exposure, increased heart weights were noted. In repeated dose studies in the dog, administration of ODV, at similar exposure levels, was associated with ECG changes (prolonged PR intervals and/or 1st degree AV block, prolonged QRS and QT intervals) and decreased heart rate. Echocardiography was performed in the 26-week toxicity study in the dog and revealed progressive left ventricular dilatation, eccentric hypertrophy and minor reduction in ejection fraction (the latter within normal reference range) associated with increased stroke volume while the cardiac index was not affected.

All cardiac findings were found to be reversible or partially reversible.

For more information refer to the Investigator's Brochure and its addendum.^{15,44}

Evaluation of the results from an additional 8-week repeat dose (70 mg/kg orally) mechanistic study in the telemetered dog is currently ongoing with details to be included in the preclinical study report. In this study ODV was administered at a dose approximately 200 times higher than the dose planned for the current study HPC2001. Preliminary data showed a decrease in cardiac contractility, resulting in a decrease in ejection fraction and systolic and diastolic blood pressure. The increase of PR/PQ interval preceded an increase in ventricular mass. QT interval increased later in the study. Information of exposure levels achieved with this dose, biomarker data and histopathology are pending and will be included in the final study report. The clinical relevance of the above findings is not yet completely understood. Importantly, analysis of all available echocardiography assessments from clinical studies in humans has not shown safety signals to date (see below).

Summary of cardiac safety in humans

A total of 440 subjects, of whom 75 were HCV infected subjects and 365 were healthy subjects (ie, non-HCV infected subjects), had initiated treatment with ODV alone or in combination with DAAs other than AL-335 and SMV. These included therapeutic Phase 2 studies of up to 12 weeks in duration where ECG and echocardiography were performed for cardiac safety monitoring. No notable effects on mean PR, QRS, or QT interval corrected for heart rate according to Fridericia (QTcF)¹¹ values over time were noted and there were no clinically significant findings identified in the echocardiograms.

In these completed studies, in study ACH102-005 a treatment-emergent PR prolongation was observed; this event evolved to a transient type 1 second-degree AV block at Week 12. The cardiologist assessed the subject's second-degree AV block to be of undetermined etiology but unlikely due to study drug. The subject completed the full course of 12 weeks therapy with ODV and RBV. Based on the currently available data the cardiac safety profile of ODV is considered acceptable to conduct the present study.

In addition, data are available from 2 studies evaluating ODV in combination with AL-335 with or without SMV (completed DDI Study AL-335-602 in healthy volunteers and ongoing Phase 2a Study AL-335-604 in HCV infected subjects). In Study AL-335-602, 32 healthy volunteers received AL-335+ODV±SMV. As of 22 June 2016, 97 subjects in Study AL-335-604 had been

enrolled and had received at least 1 dose of study medication. One SAE of asymptomatic second-degree Mobitz type 1 AV block was reported (Week 5 of treatment) in a subject in Study AL-335-604 with a borderline elevated PR interval at screening. The subject received study treatment with AL-335 400 mg qd + ODV 50 mg qd + SMV 150 mg qd. The event led to discontinuation of the study drugs (AL-335, ODV, and SMV) and was considered probably related to ODV and possibly related to AL-335 and SMV by the investigator. Echocardiography remained normal and the event was considered a benign conduction disorder which appeared to have settled 4 days after study drug discontinuation, and no further investigations were considered needed. In study AL-335-604, an additional subject had an elevated PR interval (mean: 234 milliseconds) at baseline which did not change significantly post baseline (maximum mean: 257 milliseconds). This was not considered a treatment-emergent AE, however, in light of the Wenckebach SAE described above, ODV was discontinued in this subject as a precaution at study Week 5. The subject continued AL-335 and SMV through Week 8.

Continued surveillance of cardiac safety will be done in this Phase 2b study via assessments of AEs and serial ECGs and regular echocardiograms, which will be obtained at specified time points during the treatment and follow-up period (see the [Time and Events Schedule](#)). In addition, a toxicity management plan for cardiac events (see Section 9.8.6.7) and study treatment stopping rules (see Section 6.4) taking into account cardiac safety data of all ongoing studies including ODV as part of the regimen are included in the protocol. Finally, concomitant use of medications with a potential to prolong QT interval (eg, digoxin as well as ion channel blockers) are disallowed from screening until the end of the study unless this regimen is chronically administered at a stable dose with no detectable prolonging effect on QT interval or initiation of the medication is necessary to protect subject safety and the case has been discussed with the sponsor (for details see Section 8).

Potential Risks for SMV

- **Hepatic Decompensation and Hepatic Failure:**

Hepatic decompensation and hepatic failure, including fatal cases, have been reported post-marketing in patients treated with SMV in combination with PegIFN/RBV and in combination with SOF. Most cases were reported in patients with advanced and/or decompensated cirrhosis who are at increased risk for hepatic decompensation or hepatic failure. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between treatment with SMV and these events has not been established. In clinical studies of SMV, modest increases in bilirubin levels were observed related to the inhibition by SMV of bilirubin transporters (OATP) without impacting hepatic function and were generally not associated with elevations in liver transaminases.

Potential Risks for AL-335, ODV, and SMV

The following potential risks will be carefully monitored during the study and are specified in this protocol:

- **Reproductive Risks and Pregnancy:**

No studies have been performed with AL-335, ODV, and SMV in pregnant women.

The effect of AL-335 on reproduction and development is not known. Participation in clinical studies including AL-335 requires a subject and his or her partner to, between them, use 2 effective methods of birth control.

There was no maternal toxicity and no effects on embryo/fetal survival, growth, or external fetal morphology in rat at any ODV dose level up to the highest dose tested (150 mg/kg/day) and in rabbits at any dose level up to the highest dose tested (300 mg/kg/day).

In animal studies, SMV had no effect on fertility and early embryonic and fetal development in rats up to doses of 500 mg/kg corresponding to an exposure of 221 µg.h/mL in plasma. No human data on the effect of SMV on fertility are available. Therefore, pregnancy and breastfeeding have been exclusion criteria for all clinical studies with SMV conducted to date. Women of childbearing potential and men included in studies with SMV have been required to use effective methods of birth control.

In this study, female subjects of childbearing potential and their male partners must agree to follow the contraceptive requirements as described in Section 4.1. Female subjects' study treatment will be discontinued if they become pregnant (see Section 12.3.3). Female partners of male subjects are not allowed to be pregnant or plan on becoming pregnant (during treatment and up to 12 weeks after the EOT).

- **Drug-drug Interactions:**

An overview of disallowed concomitant medication is presented in Section 8, Prestudy and Concomitant Therapy.

Based on in vitro data, AL-335 is predicted to have a low potential for CYP450-mediated DDI. Despite a low risk for DDIs, as a precaution, subjects should not receive any medication known to be a strong inducer or inhibitor of CYP3A within 2 weeks prior to receiving AL-335 until completing AL-335 treatment.

The Phase 1 DDI study (AL-335-602) to evaluate the effect of SMV (150 mg qd) and ODV (loading dose of 150 mg followed by 50 mg qd) on AL-335 (800 mg qd) PK in healthy volunteers indicated that co-administration of all 3 study drugs (SMV, ODV, and AL-335) resulted in a 7-9-fold, 2.5- to 2.7-fold, and 1- to 1.5-fold increase in AL-335, ALS-22399, and ALS-22227 plasma exposure, respectively, compared to administration of AL-335 alone. A 2-fold increase of SMV plasma exposure and a 1.7-fold increase of ODV exposure was observed when the 3 study drugs were co-administered compared to SMV administered alone or ODV administered alone respectively.

No clinically significant DDI was observed between ODV and sovaloprevir, montelukast, atazanavir/ritonavir, efavirenz/emtricitabine/tenofovir disoproxil fumarate, darunavir/ritonavir, or raltegravir.

SMV is mainly metabolized by CYP3A enzymes. Co-administration of SMV and drugs that induce CYP3A enzymes may decrease SMV plasma concentrations and reduce its therapeutic effect. Conversely, co-administration of SMV and drugs that inhibit CYP3A enzymes may increase SMV plasma concentrations and increase or prolong its therapeutic and adverse effects.

The impact of SMV on drug-metabolizing enzymes is limited to mild inhibition of intestinal (not hepatic) CYP3A and mild inhibition of CYP1A2. In addition, interaction potential with P-gp and OATP1B1 substrates has been identified.

- **Development of Drug Resistance:**

Resistance mutations emerging during unsuccessful treatment with all oral DAA regimens have been associated with decreased susceptibility to drugs within the same DAA classes used in subsequent treatment regimens and may therefore have an impact on clinical outcome. Some subjects treated with the 3-DAA combination AL-335+ODV+SMV for a duration of 6 or 8 weeks may fail treatment due to viral relapse. Although published data^{38,39,40} from DAA combination regimens given for short durations like 6 or 8 weeks have shown that a substantial part of subjects with viral relapse fail without the emergence of resistance, there is a potential risk that subjects with virologic failure in this study may develop resistance to AL-335, ODV and/or SMV. Persistence of emergent AL-335-, ODV-, and/or SMV-resistant variants could potentially impair a subject's future treatment options due to potential cross-resistance within the respective DAA class. For subjects not achieving SVR, the sponsor will reimburse one treatment regimen with the standard of care for this population in the respective country.

AL-335

In the multiple ascending dose part of Study AL-335-601, 16 HCV genotype 1, 8 genotype 2, and 8 HCV genotype 3 infected subjects received AL-335 (400 mg or 800 mg) for 7 days and 4 genotype 1, 2 genotype 2 and 2 genotype 3 subjects received placebo for 7 days. Population sequencing of the HCV NS5B region was performed for 20 genotype 1 subjects before, during and after treatment in samples with HCV RNA levels above the limit of detection of the sequencing assay (1,000 IU/mL). The NS5B amino acid change S282T, previously identified in vitro to be associated with AL-335 resistance, was not observed by population sequencing in the genotype 1 subjects at any time point during the study. No other potential AL-335 RAVs were observed in these subjects.

Odalasvir

In the Phase 2 study ACH102-005, evaluating ODV + RBV for 12 weeks in 8 treatment-naïve subjects with HCV genotype 1b infection and *IL28B* genotype CC, there were no instances of viral breakthrough despite the presence of pre-existing mutations associated with NS5A inhibitor resistance. In two subjects a slower rate of viral load decline during treatment was observed and HCV RNA remained above the limit of quantification at EOT. In these two subjects, multiple NS5A amino acid substitutions (3 up to 6) were

detected at baseline. Three out of 6 subjects who achieved HCV RNA levels < lower limit of quantification (LLOQ) target not detected at EOT relapsed. In the subjects who experienced viral relapse, emerging mutations observed at time of failure conferred high level resistance to ODV (L28M+Y93H [n=1], L28M+Y93N [n=1], P29 deletion [n=1]) and these required at least 2 nucleotide changes.

In the Phase 2a study ACH102-007, evaluating ODV in combination with sovalprevir and RBV for 12 weeks in HCV genotype 1 infected subjects (N=30; 20 active/10 placebo) virologic failure was seen only in subjects with HCV genotype 1a, with a total of 6 viral breakthroughs and 1 relapse out of 12 genotype 1a subjects. Highly resistant mutations were detected around the time when viral breakthrough or relapse occurred in both target genes (NS3 protease and NS5A) in all subjects, with emerging NS5A mutations observed by population sequencing at NS5A positions 28, 30, 58, and/or 93. The emerging mutations in NS5A persisted through the last follow-up time point, ie, EOT + 52 weeks.

Simeprevir

In a pooled analysis of subjects with HCV genotype 1 infection, treated with SMV 150 mg qd in combination with PegIFN/RBV, who did not achieve SVR in the placebo-controlled Phase 2b and Phase 3 studies C205, C206, C208, C216, and HPC3007, emerging mutations at NS3 positions 80, 122, 155 and/or 168 were observed in 180 of 197 (91%) subjects. Mutation R155K alone or in combination with other mutations at positions 80, 122, and/or 168 emerged most frequently in HCV genotype 1a infected subjects and mutation D168V emerged most frequently in HCV genotype 1b infected subjects. Emerging mutations generally conferred high level resistance to SMV in vitro.

Follow-up of the subjects with emerging mutations at time of failure within the Phase 2b and 3 studies showed that emerging resistant variants were no longer detectable by standard population sequencing in 50.0% (90/180 subjects) of subjects within the trial period (median follow-up time 28 weeks; range: 0 to 70 weeks).

In study HPC3011 in genotype 4 infected subjects, 28 out of 32 (88%) subjects who did not achieve SVR had emerging mutations at NS3 positions 80, 122, 155, 156, and/or 168 (mainly mutations at position 168; 24 out of 32 [75%] subjects), similar to the emerging mutations observed in genotype 1 infected subjects.

In study HPC3005, paired baseline and failure NS3 sequencing information was available for 13 of the 32 subjects with treatment failure in the SMV arms (6 subjects in the SMV100/PegIFN/RBV arm and 7 subjects in the SMV150/ PegIFN/RBV arm), all of whom were infected with HCV genotype 1b. The majority of subjects with treatment failure and sequencing data available had emerging mutations at NS3 position 80 and/or 168 (76.9% [10 of 13 subjects]). Nine out of the 10 subjects with emerging mutations had emerging D168V.

In the Japan Phase 3 studies (SMV 100 mg qd) the NS3 sequencing data showed that most subjects with treatment failure (75.0% to 92.9% depending on prior treatment history) had

emerging resistance mutations (R155K in subjects with HCV genotype 1a and primarily D168V in subjects with HCV genotype 1b) in the NS3 protease domain. In many subjects, these mutations detected at the time of treatment failure were not detected anymore by the end of the study.

The majority of HCV genotype 1 infected subjects treated with SMV and SOF (with or without RBV) for 12 or 24 weeks who did not achieve SVR12 and with sequencing data available had emerging NS3 mutations at position 168 and/or an emerging R155K mutation: 5/6 subjects in study HPC2002, 1/3 subjects in study HPC3017 and 11/13 subjects in HPC3018. The emerging NS3 amino acid substitutions were similar to those observed in subjects who did not achieve SVR following treatment with SMV in combination with PegIFN/RBV.

In contrast, the majority of subjects experiencing viral relapse following 8 weeks of treatment with SMV and SOF in study HPC3017 had no emerging NS3 mutations reducing SMV activity in vitro at the time of failure.

The long-term clinical impact of the emergence of SMV-resistance associated mutations is unknown.

1.3.3. Overall Benefit/Risk Assessment

Based on the available data and proposed safety measures, the overall risk/benefit assessment for this clinical study is acceptable for the following reasons:

- The toxicology profile for AL-335, established in multiple in vitro and in vivo studies. Data from a Phase 1 study in healthy volunteers and HCV infected subjects with AL-335 800 mg qd for 7 days, as well as a Phase 1 study (AL-335-602) in healthy volunteers and an ongoing Phase 2a study (AL-335-604) in HCV infected subjects provide evidence that AL-335 has an acceptable safety profile.
- ODV safety results from the completed and ongoing clinical studies, along with results from the nonclinical toxicology studies provide preliminary evidence that ODV is generally safe and well tolerated. Given available nonclinical and clinical data, cardiac monitoring is conducted through serial ECGs and regular echocardiograms throughout the treatment period and follow-up (see the [Time and Events Schedule](#)). In addition, a toxicity management plan for cardiac events is included in the protocol (see Section 9.8.6.7) and all concomitant medications with a potential to prolong QT interval (eg, digoxin as well as ion channel blockers) are disallowed from screening until the end of the study (see Section 8).
- SMV safety data from Phase 1, 2, and 3 studies showed that SMV was generally safe and well tolerated in healthy and HCV infected adults at all doses tested. Phase 2 and 3 studies showed that dosing with SMV 100 mg and 150 mg qd for 12 weeks in combination with PegIFN/RBV for 24 or 48 weeks and SMV in combination with SOF with or without RBV was safe and well tolerated in HCV infected subjects.

- Data from the Phase 2a study AL-335-604 in HCV infected subjects, including interim PK and safety data, were reviewed and guided the selection of the AL-335 dose in the present study (see Sections 1.2 and 3.2 for details). The target doses for the individual study drugs are 800 mg qd for AL-335, 25 mg qd for ODV, and 75 mg qd for SMV.
- Only subjects who meet all of the inclusion criteria and none of the exclusion criteria (as specified in Section 4) will be allowed to participate in this study. The selection criteria include adequate provisions to minimize the risk and protect the well-being of subjects in the study.
- Safety will be closely monitored throughout the study. Safety and tolerability assessments (including vital signs, physical examination, ECG, echocardiography and clinical laboratory tests) will be performed at scheduled visits throughout the study until the follow-up visit 24 weeks after the actual EOT. Adverse events will be collected from signing of the informed consent form (ICF) until the subject's last study visit. All collected AEs and SAEs will be followed until satisfactory resolution (eg, value returns to baseline value) or stabilization (to be agreed upon in collaboration with the sponsor). Pregnancies will be reported until end of study.
- Regular review of HCV RNA data by a Data Review Committee (DRC) is implemented to allow for prompt determination of suboptimal efficacy due to virologic failure (viral relapse and/or on-treatment virologic failure). The DRC will also review accumulating safety data from this study as well as emerging safety and efficacy data from other completed and ongoing studies, including the Phase 2a study AL-335-604.
- Several safety measures have been proposed to minimize potential risk to subjects, including:
 - The safety monitoring and toxicity management plan in this study (see Section 9.8.6), which takes into account AEs based on toxicities of AL-335, ODV, and SMV, clinical safety data of ODV and SMV, target organs identified in nonclinical studies, and toxicities reported for nucleotide analogs.
 - Individual subject treatment stopping rules for viral breakthrough and specific toxicities (see Section 6.3 and Section 10.2, respectively)
 - Study treatment stopping rules that terminate further enrollment and dosing of all subjects in the study based on pre-specified cardiac safety information from any ongoing study using ODV (see Section 6.4),
 - Prohibitions and restrictions related to pregnancy and photosensitivity (see Section 4.3).
 - Predefined safety-related criteria detailed in Section 10.2 require subjects to discontinue all study drugs (AL-335, ODV, and SMV).

- For subjects who do not achieve SVR the sponsor will reimburse one treatment regimen with the standard of care for this population in the respective country.
- If a subject withdraws from the study (ie, withdrawal of consent), he/she maintains the option to participate in the safety follow-up procedures.

1.4. Overall Rationale for the Study

While DAA combination treatment has led to high SVR with a good safety profile, there remains an unmet medical need for alternative effective, safe, shorter, and simpler treatment regimens that can be used in all HCV infected patient subgroups, regardless of genotype or baseline prognostic factors. This Phase 2b study investigates a 3-DAA combination of AL-335 (HCV NS5B inhibitor), ODV (a second generation HCV NS5A inhibitor), and SMV (HCV NS3/A4 inhibitor) directed at 3 different targets in the HCV life cycle, respectively. It is anticipated that an all-oral, qd, 3-DAA combination of AL-335, ODV, and SMV may allow shortening of HCV treatment duration compared to currently available treatment regimens. The aim of the study is to evaluate shorter treatment durations of 8 or 6 weeks AL-335+ODV+SMV in HCV genotype 1, 2, 4, 5 and 6 infected subjects without cirrhosis without compromising efficacy, or the subject's compliance and safety.

Available clinical data and nonclinical data for AL-335 have indicated that AL-335 has potent in vitro activity against all 6 HCV genotypes. Dosing with AL-335 for 7 days in subjects with chronic HCV genotype 1, 2, or 3 infection resulted in a rapid, consistent, dose-dependent decline in HCV RNA concentrations. ODV in combination with SOF for 6 weeks or 8 weeks resulted in high SVR rates in HCV genotype 1 infected subjects; 100% of the subjects (N=30, of which 18 were treated for 6 weeks), including subjects with HCV genotype 1a and subjects with *IL28B* genotype non-CC, achieved SVR12. Odalasvir has potent in vitro activity against all 6 HCV genotypes. SMV has antiviral activity against HCV genotypes 1, 2, 4, 5, and 6, and is approved in several countries/regions in combination with PegIFN/RBV and in combination with SOF for the treatment of HCV genotype 1 or 4 infected patients with or without HIV co-infection and with or without cirrhosis.

The toxicology profile for AL-335, established in multiple in vitro and in vivo studies and safety data from a Phase 1 study in healthy volunteers, provides evidence that AL-335 has an acceptable safety profile. The safety and tolerability of ODV has been and is being studied in Phase 2 (chronic HCV infected subjects) and Phase 1 studies (healthy volunteers) and these studies provide evidence that ODV is generally safe and well tolerated. The safety and tolerability of SMV in combination with PegIFN and RBV or with SOF has been established in HCV infected subjects with and without cirrhosis and in subjects co-infected with HIV.

While in the Phase 2a study AL-335-604, the SVR12 was high in both the 3- and 2-DAA arms, preliminary data support the use of a 3-DAA regimen with AL335 800 mg + ODV 25 mg and SMV 75 mg to maximize SVR when evaluating short treatment durations of 6 and 8 weeks.

The present Phase 2b study is designed to evaluate the efficacy, safety, tolerability and PK of a 6- and 8-week treatment regimen consisting of AL-335, ODV, and SMV in treatment-naïve and

treatment-experienced subjects with chronic HCV genotype 1, 2, 4, 5 or 6 infection without cirrhosis. Data from the DDI study, AL-335-602, in 32 healthy volunteers, evaluating 800 mg AL-335 which was either administered alone or co-administered with 150 mg SMV and/or 50 mg ODV, indicated that SMV when given on top of ODV led to a significant increase in AL-335 exposure (7- to 9-fold) and metabolite ALS-022399 exposure (2.5- to 2.7-fold), and a slight increase in metabolite ALS-022227 (1- to 1.5-fold). In vitro, AL-335 is a clear substrate for the intestinal P-gp efflux pump and SMV is a clinically confirmed P-gp inhibitor (increased exposure of digoxin in presence of SMV). The observed boosting effect of SMV on the plasma levels of AL-335 as well as the mechanism of P-gp inhibition could lead to an increase in the bioavailability of AL-335 and subsequently higher intrahepatic triphosphate levels in liver cells of HCV infected subjects and an enhanced antiviral activity of AL-335. In addition, at the selected dose of AL-335 800 mg, a rapid and consistent decline in HCV RNA concentrations has been observed (multiple ascending dose cohorts in Study AL-335-601).

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

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

Secondary Objectives

The secondary objectives are:

- 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 a 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 PK of 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, AUC_{24h} and predose plasma concentrations [C_{0h}]) 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

The exploratory objectives are:

- 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 RNA level, genetic factors (eg, *IL28B*), 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 (PCS) and Mental Component Summary (MCS) 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).

2.2. Hypothesis

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

Statistical testing will be conducted using null hypothesis $H_0: C-T \geq 10\%$ vs. $H_a: C-T < 10\%$ at a significance level of 0.05, 2-sided, where C is the historical control rate of 98% and T is the expected SVR rate in the treatment arm.

For more information, see Section [11.3](#).

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 2b multicenter, randomized, open-label, study to investigate the efficacy, safety and PK of a 6- and 8-week treatment regimen with AL-335, ODV, and SMV followed by a 24-week post-treatment follow-up in treatment-naïve and treatment-experienced subjects with chronic HCV genotype 1, 2, 4, 5 or 6 infection without cirrhosis.

The study will include a screening period of maximum 6 weeks starting from the time of first screening assessment. In exceptional cases, the screening phase can be extended if discussed with and approved (documented) by the sponsor. Thereafter, if eligible, subjects will be randomized to receive AL-335, ODV, and SMV for either 6 or 8 weeks. A post-treatment follow-up until 24 weeks after the actual EOT is included to assess SVR12 and SVR24. The total study duration for each subject will be approximately 36 to 38 weeks (including the 6-week screening period, the 6- or 8-week treatment periods and the 24-week post-treatment follow-up period); the 6- and 8-week treatment periods can be extended to treatment periods of maximum 12 weeks upon recommendation by the DRC. The study is considered completed with the last visit of the last subject participating in the study.

A target of approximately 300 male or female subjects, aged 18 to 70 years (extremes included), with HCV genotype 1, 2, 4, 5 or 6 infection and with HCV RNA >10,000 IU/mL are planned to be enrolled in the study. Subjects with cirrhosis or liver disease of non-HCV etiology, including hepatitis B co-infection will be excluded. Subjects volunteering to participate, having signed the ICF, and found eligible for the study at screening, will be required to discontinue specified disallowed medication (as specified in the list of disallowed medication; see Section 8).

The study will include treatment-naïve and treatment-experienced (to [Peg]IFN ± RBV) HCV genotype 1, 2, 4, 5 and 6 infected subjects without cirrhosis. Subjects who participate in this study will be classified as treatment-naïve, defined as not having received prior treatment with any approved or investigational drug (including DAAs, IFN-based treatments and vaccines) for chronic HCV infection or treatment-experienced, defined as having received HCV therapy consisting of IFN (pegylated or non-pegylated) with or without RBV. Subjects who have prior experience with any anti-HCV DAA-based regimen or all-oral DAA regimen are excluded from the study.

The dose of SMV will be 75 mg qd, the dose of ODV will be 25 mg qd and the dose of AL-335 will be 800 mg qd. For more information on the dose selection, see Section 3.2.

Approximately 300 treatment-naïve and –experienced (to [Peg]IFN ± RBV) chronic HCV genotype 1, 2, 4, 5 or 6 infected subjects without cirrhosis will be randomized (in a 1:1 ratio) to one of the following treatment arms:

- Arm A (N=150): AL-335 800 mg qd + ODV 25 mg qd + SMV 75 mg qd for 6 weeks
- Arm B (N=150): AL-335 800 mg qd + ODV 25 mg qd + SMV 75 mg qd for 8 weeks

Patients still in screening at the time of reaching the target enrollment in the study were allowed to enroll when proven eligible after completion of the screening procedures, leading to the enrollment of an additional 65 subjects in the study (365 subjects in total: 183 subjects in Arm A and 182 subjects in Arm B).

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). In the stratification by HCV geno/subtype, subjects with a genotype 1 non-specifiable subtype at screening will be assigned to the 1b, 4, 5 or 6 stratification group (see Section 5). All efforts need to be made to enroll as many HCV genotype 2, 4, 5 and 6 subjects as possible.

HCV RNA levels will be processed in real time and continuously monitored by the sponsor and communicated to the investigator throughout the study. Subjects will be monitored from Day 1 through end of follow-up for viral breakthrough or relapse. As described in Section 11.11, Data Review Committee, review of virologic response including viral relapse will be conducted to allow for any specific recommendation including extension of treatment duration if deemed necessary based on the accumulating data. If treatment extension is recommended for the 6-week treatment duration, the 6-week treatment arm will be extended to 8 weeks. If treatment extension is recommended for the 8-week treatment duration, the 6- and 8-week arms will be extended to 12 weeks. In case of observation of treatment failure, a thorough evaluation of each case will be performed to ensure that the treatment failure is not related to non-virologic reasons. For subjects who do not achieve SVR, the sponsor will provide the investigator with available HCV sequencing data. For these subjects, the sponsor will reimburse one treatment regimen with the standard of care for this population in the respective country.

Study drugs will be discontinued for subjects with viral breakthrough (ie, confirmed $>1.0 \log_{10}$ increase in HCV RNA from nadir or confirmed HCV RNA >100 IU/mL in subjects who had previously achieved HCV RNA $<LLOQ$).

A DRC will be established to monitor data on a regular basis to ensure the continuing safety, efficacy and well-being of the subjects enrolled in this study (see Section 11.11). The DRC is a committee within the sponsor's organization that is independent of the sponsor's study team. Virologic failures will be communicated immediately to the DRC to trigger efficacy review. Emerging safety and efficacy data from this study will be reviewed at predetermined intervals. As a part of the safety evaluations, the DRC will also review AEs considered anticipated events for this patient population (see Attachment 8).

Upon review of the HCV RNA data from this study and/or consideration of data from other completed and ongoing studies, including the Phase 2a study AL-335-604, the DRC will make study conduct recommendations, which may include but are not limited to, continuing the study without modifications and/or implementation of treatment extension. The sponsor's decision based on the recommendation will be communicated to the investigator. Details will be specified in a separate charter.

In case of treatment extension, subjects will continue to attend study visits every 2 weeks. In case of treatment extension to 8 weeks, the subjects should follow the visit schedule of subjects initially included in the 8-week treatment arm, with an EOT visit at Week 8. In case of treatment extension to 12 weeks, subjects should follow the schedule for the 12-week treatment extension arm with an EOT visit at Week 12.

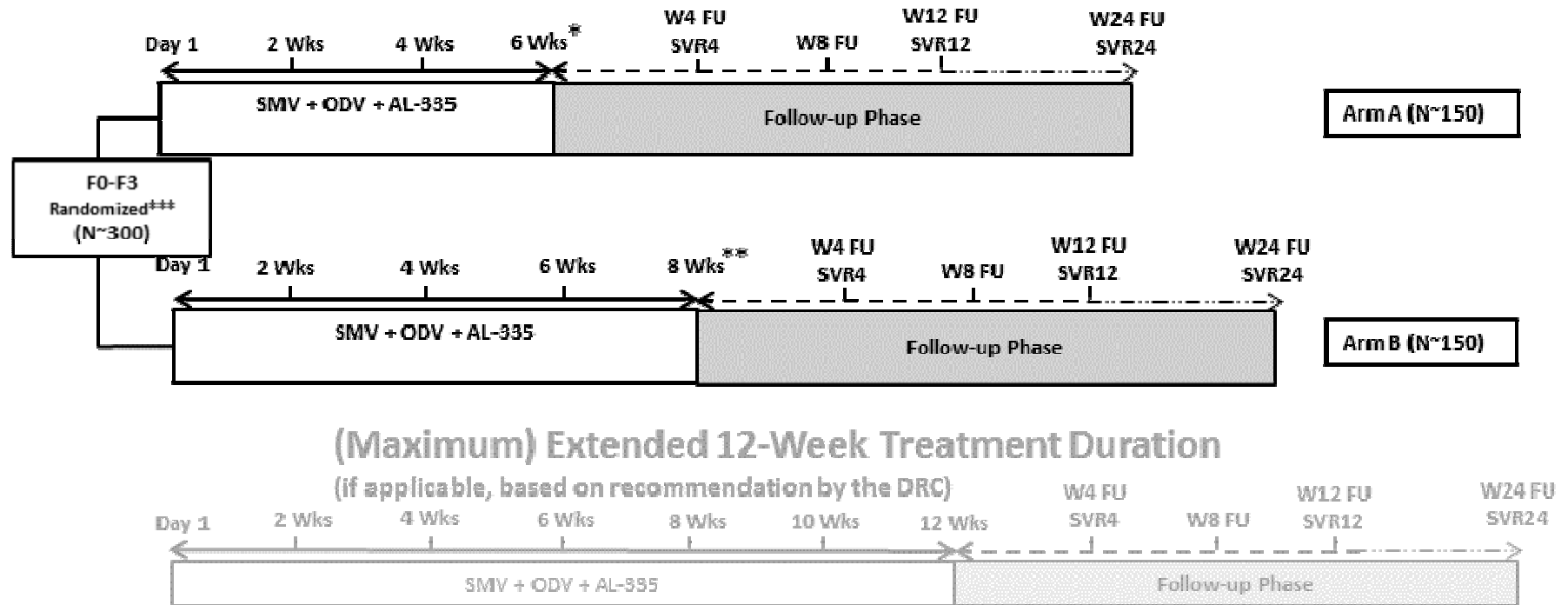
In case of substantial changes to the study conduct, other than the treatment prolongation described above, an amendment to the current protocol will be submitted for approval by the competent authorities.

If study drug treatment is discontinued prematurely, for reasons other than withdrawal of consent, a treatment withdrawal visit should be scheduled as soon as possible after the EOT. The subjects will be followed-up for 24 weeks after EOT, with visits as indicated in the [Time and Events Schedule](#). If a subject discontinues treatment due to withdrawal of consent, the subject will be offered an optional early treatment withdrawal visit, to be scheduled as soon as possible after withdrawal and/or a safety follow-up visit, which needs to be scheduled 4 weeks after EOT. At the safety follow-up visit safety assessments of the Week 4 follow-up (W4 FU) visit need to be performed. Any subject who withdraws consent during the follow-up phase and/or notifies the site he or she will not return for study visits, will be invited to do a follow-up visit at the time of withdrawal to complete the full set of protocol procedures as scheduled for the Week 24 follow-up (W24 FU) visit. However, all possible efforts should be made to ensure that subjects complete the study.

All study drugs (AL-335, ODV, and SMV) should be taken together in the morning at approximately the same time every day throughout the treatment phase and be administered with food (ie, during or no later than 15 minutes after a meal). Study drug intake should take place on site during visits when biochemistry samples are to be taken after fasting for at least 8 hours, and when pre-dose PK sampling is performed (see [Time and Events Schedule: PK Assessments in PK Substudies](#)). At visits where study drug dosing occurs on-site, study sites should have arrangements in place to offer the subjects a meal.

A diagram of the study design is provided in [Figure 1](#).

Figure 1: Schematic Overview of the Study



* If DRC recommends treatment extension, treatment will be extended to 8 weeks.

** If DRC recommends treatment extension, treatment of this arm and the 6-week arm will be extended to 12 weeks.

*** 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).

Dosage: AL-335 800 mg qd, ODV 25 mg qd, SMV 75 mg qd

N: planned number of subjects; ODV: odalasvir, SMV: simeprevir, Wks: weeks

Assessments

The baseline visit (Day 1) may be scheduled as soon as the results of all screening assessments are known (but should occur within 6 weeks from the first screening assessment) and show that the subject is eligible for inclusion. Study drug intake will start on Day 1, after the completion of the baseline assessments (except for the second blood sample to be taken within 4 hours post dose for the post-dose HCV RNA determination).

Efficacy of the regimen will be assessed by means of HCV RNA levels (see Section 9.2.1.1) and ALT/AST levels (part of biochemistry testing battery; see Section 9.2.1.2); samples will be collected throughout the study. For resistance determination, blood samples will be collected throughout the study (see Section 9.2.1.3).

The impact of HCV and its treatment (safety and efficacy) on patient-reported symptoms, functioning and HRQoL (PRO, see Section 9.2.1.4) will be assessed at selected time points throughout the study. In addition occupational/employment status (see Section 9.6) and MRU (see Section 9.7) will be assessed.

Pharmacokinetic samples will be taken at any time during the visit for all subjects at the Week 4 visit, the Week 6 visit (arm B) and at the EOT visit. At the EOT visit, subjects should still be on treatment at the time of the PK assessments (the last dose is expected to be taken on the morning of the visit). In addition, at selected sites, a rich PK substudy and a sparse PK substudy will be performed in subsets of subjects (ie, 20 subjects from arms A and B combined in each of the PK substudies; see Section 9.3).

One mandatory pharmacogenomic blood sample will be collected at baseline to allow for the determination of the subject's *IL28B* genotype (rs12979860). Where locally permitted and upon consent of the subject (in addition to the consent for the main part of the study), an additional optional blood sample may be collected preferentially at baseline for host DNA research (see Section 9.5) related to AL-335 (and metabolites), ODV, and SMV, and limited to genes involved in the metabolism of the study drugs as well as drug transporter genes.

The safety evaluations will include the monitoring of AEs, clinical laboratory tests, ECGs, echocardiograms, vital sign measurements, physical examinations, and specific toxicities (see Section 9.8).

Subjects will complete all above mentioned assessments during study-related visits as specified in the [Time and Events Schedule](#).

An interim analysis is planned at the SVR4 time point, ie, when all subjects have reached the SVR4 (W4 FU visit) time point or discontinued earlier.

The primary analysis will be performed when all subjects have reached the SVR12 time point (W12 FU visit) or discontinued earlier. The final analysis will be performed when all subjects have completed the last study-related visit (SVR24 time point; W24 FU visit) or discontinued earlier. Additional interim analyses may be conducted if needed to support clinical development.

Safety, efficacy, and/or pharmacokinetic data from this study may be pooled with data from the Phase 2a AL-335-604 study and potentially other similarly performed studies to assess the combination regimen of AL-335, ODV and SMV. This will increase the sample size for the different subgroups/duration groups and provide for more accurate estimates for safety and efficacy endpoints. The details of this combined analysis will be outlined in a separate analysis plan.

3.2. Study Design Rationale

Dose and Treatment Duration

The present study will evaluate a 3-DAA regimen of AL-335 800 mg, ODV 25 mg, and SMV 75 mg, co-administered qd with food (as individual tablets/capsules) in the morning for 6 or 8 weeks.

An optimal IFN-free regimen for treatment of chronic HCV infection requires a combination of agents with different mechanisms of action. Available data suggest that addition of a third anti-HCV agent to a 2-DAA regimen may increase the robustness of the regimen to allow for a shorter treatment duration compared to currently available treatment regimens while maintaining high efficacy. The study population of the current study will include (IFN-based) treatment-naïve and -experienced subjects without cirrhosis across HCV genotypes 1, 2, 4, 5 and 6.

Selection of Doses

AL-335 dose selection

At the time of the AL-335 dose selection for the current study, preliminary PK data from the Phase 1 DDI study AL-335-602 with SMV (150 mg qd), ODV (loading dose of 150 mg followed by 50 mg qd) and AL-335 (800 mg qd) in healthy volunteers suggested SMV and ODV individually and combined increase AL-335 (prodrug) exposure (AL-335 AUC increased 3- to 4-fold with SMV or ODV and 7- to 8-fold with SMV+ODV). Modest increases in plasma exposure (AUC) are also observed in the AL-335 prodrug metabolite ALS-0022399 (2.6- to 2.8-fold) with little to no effect on the AL-335 parent nucleoside metabolite ALS-0022227 when AL-335 is combined with SMV and/or ODV. The parent nucleoside is the major circulating drug-related moiety.

The objective of the ongoing Phase 2a study AL-335-604 is to enable selection of a dose and regimen with optimal risk/benefit profile for the Phase 2b study. In each cohort, the PK, safety, and efficacy of the orally administered combinations of AL-335 and ODV with or without SMV are evaluated. Based on the DDI study in healthy volunteers (AL-335-602), the first cohort was dosed with SMV 100 mg qd, ODV 50 mg qd and AL-335 400 mg qd for 8 weeks. The PK data from this first cohort of Study AL-335-604 indicated that at the 400-mg dose of AL-335, plasma levels of the parent nucleoside metabolite were similar to that observed in the monotherapy study AL-335-601 at the 400-mg dose and the increase in pro-drug AL-335 in the presence of ODV and SMV (AL-335-602) did not translate into increases of the parent nucleoside of AL-335. In the AL-335-601 study, 7 days of AL-335 monotherapy showed in HCV genotype 1-infected patients a greater magnitude of HCV RNA decline from baseline at 800 mg qd compared to that

observed with 400 mg qd (mean maximum decrease in HCV RNA from baseline of 4.00 log₁₀ IU/mL for the 800-mg dose compared to 2.76 log₁₀ IU/mL for the 400-mg dose). In addition, 7 days of monotherapy with AL-335 at 800 mg qd in HCV genotype 2- and genotype 3-infected patients showed potent suppression of viral replication with a mean maximum decrease in HCV RNA from baseline of 4.46 log₁₀ IU/mL and 4.72 log₁₀ IU/mL for genotype 2 and genotype 3, respectively. Therefore, the selected dose of AL-335 for subsequent cohorts in the Phase 2a study AL-335-604 and for use in the current Phase 2b study is 800 mg qd.

AL-335 was generally well tolerated at single doses up to 1,200 mg by healthy volunteers and for multiple doses of 400 mg and 800 mg administered as monotherapy in HCV infected subjects for 7 days (Study AL-335-601). There were no related SAEs, and no clinically relevant laboratory, ECG, Holter, vital sign, or physical exam safety signals were identified when AL-335 was administered as monotherapy. Preliminary safety evaluation of the first 97 subjects who were dosed for 6 or 8 weeks (Cohort 1, 1b, 2 and 3; 20 subjects each) or received at least 1 dose of study medication (Cohorts 4 [N=5], 5 [N=5] and 6 [N=7]) with AL-335 and ODV with or without SMV in the ongoing Phase 2a study AL-335-604 revealed no safety signals in AE, laboratory, ECG, cardiac echo, vital signs, or physical examination. One cardiac-related SAE was reported in a patient with progressive prolongation of PR interval and development of type 1 AV block (Wenckebach) (see Section 1.3.2.2 for details).

ODV dose selection

In the proof-of-concept Phase 1b study evaluating a single dose of ODV at 25 mg, 50 mg, 150 mg, or 300 mg in genotype 1 infected patients, potent antiviral activity was demonstrated for all doses.

At the time of the ODV dose selection for the current study, preliminary data from both the DDI study AL-335-602 and the ongoing Phase 2a study AL-335-604 indicated that multiple doses of the new tablet formulation used in these studies resulted in higher exposure levels of ODV than those observed with the liquid-filled capsule (LFC) formulation that was used in previous ODV studies. In the Study ACH102-017, ODV C_{max} and trough plasma concentration (C_{trough}) at steady-state after a 50-mg qd dose (LFC formulation, no loading dose; administered in fasted state) was 182 and 108 ng/mL and 214 and 132 ng/mL, respectively, in groups 1 and 2. In Study AL-335-602, the C_{max} and minimum plasma concentration (C_{min}) for ODV 50 mg (tablet formulation, 150 mg loading dose; administered in fed state [standard meal]) qd alone after 10 days of dosing was 582 ng/mL and 235 ng/mL, respectively. In order to match the exposures to the exposures observed in Study ACH102-017, the ODV dose was lowered to 50 mg every other day in the ongoing cohorts of Phase 2a study AL-335-604 and will be 25 mg qd in the current Phase 2b study.

SMV dose selection

Although SMV exposure was increased by 1.6-fold when administered in combination with ODV compared to SMV administered alone or ODV administered alone in the DDI study AL-335-602 (preliminary data available at the time of the SMV dose selection in the current

study) in healthy volunteers, results from the ongoing Phase 2a study AL-335-604 indicated that there is no significant interaction when these compounds are administered to HCV patients. In Phase 2b study C205 of SMV in combination with PegIFN/RBV, SMV doses of 75 mg and 150 mg were evaluated in treatment-naïve HCV infected subjects; no significant difference in SVR rates was observed between 75 mg and 150 mg doses of SMV and only a trend for higher SVR was observed with the SMV 150 mg dose in some difficult-to-cure subpopulations. However, in the context of an IFN-free 3-DAA regimen in which SMV is administered in combination with 2 other potent DAAs, it is hypothesized that 75 mg will provide optimal efficacy when administered along with AL-335 and ODV. In addition, SMV at a lower 75 mg dose is expected to be associated with a lower frequency of events such as increases in bilirubin, rash, and photosensitivity, which are well known to correlate with SMV exposure. In addition, the potential risk of higher exposures of ODV due to drug interactions with SMV is anticipated to be lower when SMV is administered at the dose of 75 mg.

Taking into account the dose selection rationale described above, the doses for AL-335, ODV, and SMV in the current Phase 2b study will be 800 mg qd, 25 mg qd, and 75 mg qd, respectively.

Selection of Treatment Duration

This study investigates the safety and efficacy of two different treatment durations. The 3-DAA combination of AL-335, ODV, and SMV will be given for 8 or 6 weeks.

Ideally, an IFN-free regimen for treatment of chronic HCV infection combines agents with different mechanisms of action.

Available data suggest that addition of a third anti-HCV agent to a 2-DAA regimen may increase the robustness of the regimen to allow for a shorter treatment duration compared to currently available treatment regimens while maintaining high efficacy, particularly when considering more difficult-to-cure patients.

ODV in a 2-DAA combination with SOF demonstrated an efficacy of 100% SVR in treatment-naïve HCV genotype 1 infected subjects without cirrhosis (Study ACH102-017) with a treatment duration of 8 weeks (12 subjects) and 6 weeks (18 subjects). Given the high SVR rates achieved with the 2-DAA combination with a treatment duration of 8 weeks and 6 weeks, it is anticipated that the addition of a 3rd DAA, resulting in a regimen including 3 DAAs with a different mechanism of action, will provide a robust HCV treatment regimen, also at short treatment durations, ie, 6 or 8 weeks of total treatment. In study AL-335-604, the SVR24 rate in treatment-naïve, HCV genotype 1 infected subjects without cirrhosis treated with AL-335 400 mg qd, ODV 50 mg qd, and SMV 100 mg qd for 8 weeks, was 100% (20/20 subjects). Of the 40 subjects in Cohort 2 and Cohort 3 dosed with AL-335 800 mg qd, ODV 50 mg qd, and SMV 75 mg qd for 8 or 6 weeks, respectively, all subjects achieved SVR12 and SVR4, respectively.

Study Population

A number of IFN-free DAA combination regimens have been approved mainly for the treatment of HCV genotype 1 and 4 infected patients, and recently also for genotype 2, 3, 5, and 6 HCV infected patients.

Availability of multiple agents that can interrupt several steps of the HCV lifecycle affords providers and patients with options that can be combined and individually tailored to each patient's unique needs to obtain high rates of SVR.

The pan-genotypic activity of both the NS5A inhibitor ODV and the nucleotide NS5B inhibitor AL-335, as observed from the in vitro data (see Section 1.1.4 and 1.1.3, respectively), is expected to provide in combination with SMV an effective treatment for HCV genotypes 1-6 infected patients.

This study will include treatment-naïve and treatment-experienced subjects (received prior treatment consisting of IFN [pegylated or non-pegylated] with or without RBV) with HCV genotype 1, 2, 4, 5 and 6 without cirrhosis.

Plasma levels of drugs are known to vary among races or ethnic subpopulations. Therefore we are collecting information on race upon voluntary consent of the subjects. Subjects of East-Asian origin are known to have higher plasma levels of SMV as compared to Caucasian subjects. No information is available yet on the PK of AL-335 and its metabolites and ODV in subjects of East-Asian origin. In order to accurately measure the impact of race and ethnicity on plasma exposures of AL-335 and its metabolites, ODV, and SMV when given in combination in this study, the present study will document whether subjects participating in the study are of East-Asian origin, defined as subjects whose parents and maternal and paternal grandparents are Japanese, Chinese, Taiwanese, or Korean, as determined by subject's verbal report.

Stratification Factors

The randomization will be balanced by using randomly permuted blocks and will be stratified by two important baseline factors: HCV treatment history (treatment-naïve versus treatment-experienced) and HCV geno/subtype (genotypes 1a or 2 versus genotypes 1b, 4, 5 or 6). In the stratification by HCV geno/subtype, subjects with a genotype 1 non-specifiable subtype at screening will be assigned to the 1b, 4, 5 or 6 stratification group.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 6 weeks before administration of the study drug. In exceptional cases, the screening phase can be extended if discussed with and approved (documented) by the sponsor, eg, if not all the test results become available during the allocated 6 weeks; this will be evaluated on a case-by-case basis.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the

investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

Approximately 300 subjects were planned to be enrolled in the study and, in total, 365 have been enrolled. For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination. All efforts need to be made to enroll as many HCV genotype 2, 4, 5 and 6 subjects as possible.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Man or woman, 18 to 70 years of age, inclusive.
2. Body mass index (BMI; weight in kg divided by the square of height in meters) of 18.0 to 35.0 kg/m², inclusive.
3. Documented chronic HCV infection: diagnosis of HCV infection >6 months before the first screening assessment, either by detectable HCV RNA, an HCV positive antibody test or presence of histological changes consistent with chronic hepatitis in a liver biopsy.
- 4.1 All subjects must have HCV genotype 1, 2, 4, 5 or 6 infection, determined at screening.
- 5.1 Inclusion criterion 5 was removed per the HPC2001 protocol amendment 2.
6. HCV RNA plasma levels >10,000 IU/mL for all subjects.

Note: genotype and HCV RNA plasma levels will be determined by the central lab at screening. In case of discrepancy between previously documented geno/subtype and the geno/subtype determined at screening, the screening results will be used.

- 7.1 HCV treatment-naïve, defined as not having received treatment with any approved or investigational drug (including DAAs, IFN-based treatments, and vaccines) for chronic HCV infection, or previously treated subjects (treatment-experienced) defined as having received HCV therapy consisting of IFN (pegylated or non-pegylated) with or without RBV.
8. A woman of childbearing potential must have a negative serum (β -human chorionic gonadotropin) pregnancy test at screening.
- 9.2 Contraceptive use by women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies if these are stricter than what is proposed in these inclusion criteria.

female subjects must either:

- be not of childbearing potential:
 - postmenopausal for at least 12 months (ie, 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 (eg, 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). Oral hormone-based contraceptives are not allowed from 14 days before baseline until 4 weeks after the EOT. An IUD, being either hormonal (ie, IUS*) or non-hormonal, is considered highly effective and reliable, therefore subjects are not required to use additional contraceptive methods (no double barrier method required). Other non-oral hormone based contraception methods (eg, injectable, implants, transdermal system, vaginal ring) may be continued, but as the interaction of the study drug with hormone-based contraception is unknown, these methods are not considered to be reliable and therefore subjects should use a double-barrier method (eg, male condom + either diaphragm or cervical cap with or without spermicide). Subjects having a vasectomized partner (confirmed sterile per verbal account of the subject) are not required to use additional contraceptive methods.

* An IUS does not rely on systemic plasma concentrations and is therefore not expected to be impacted by a potential DDI.

Note 1: *Sexual abstinence is considered a highly effective method **only** if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*

Note 2: *A male and female condom should not be used together due to risk of breakage or damage caused by latex friction.*

10. Willing and able to comply with the protocol requirements, including the Prohibitions and Restrictions described in Section 4.3.
11. 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.
12. Each 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.
- 13.1 Subjects without cirrhosis (absence of cirrhosis) defined as any of the following:
 - 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).

Note liver biopsy should only be considered as an alternative in subjects where Fibroscan is not feasible
14. 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.
15. Female subject must have a negative highly sensitive urine pregnancy test at Day 1.
16. Contraceptive use by men should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies if these are stricter than what is proposed in these inclusion criteria.

Male subject must either:

- be surgically sterile (had a vasectomy), or otherwise incapable of fathering a child,
- OR
- be not heterosexually active (eg, abstinence) from enrollment (Day 1) in the study until at least 12 weeks after the EOT, OR
 - if heterosexually active have a partner who is postmenopausal (2 years 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
 - if heterosexually active with a woman of childbearing potential, be practicing an acceptable method of birth control from enrolment in the study (Day 1) 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). An acceptable method of birth control for male subjects is a double-barrier method (eg, male condom + either diaphragm or cervical cap with or without spermicide). Male subjects with a female partner who uses hormonal contraceptives (oral, injectable, implants) or an hormonal (IUS) or non-hormonal IUD and male subjects who are vasectomized or otherwise incapable of fathering a child are not required to use additional contraceptive methods.

Note 1: Sexual abstinence is considered a highly effective method **only** if defined as

refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.

Note 2: *A male and female condom should not be used together due to risk of breakage or damage caused by latex friction.*

17. Male subjects must agree not to donate sperm during the study until 12 weeks after the EOT (or longer, if dictated by local regulations).

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Co-infection with multiple HCV genotypes.
2. Co-infection with HIV.
- 3.1 Presence of cirrhosis.
4. Prior exposure to an HCV DAA, either in combination with PegIFN or IFN-free.
5. Any evidence of liver disease of non-HCV etiology. This includes, but is not limited to, acute hepatitis A infection (immunoglobulin M), hepatitis B infection (hepatitis B surface antigen positive), drug- or alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, primary biliary cirrhosis, or any other non-HCV liver disease that is considered clinically significant by the investigator.
6. Evidence of hepatic decompensation (history or current clinical evidence of ascites, bleeding varices or hepatic encephalopathy).
7. Intake of any disallowed therapies as noted in Section 8.
8. History of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence of the sponsor's medical monitor, is considered cured with minimal risk of recurrence).
9. Known allergies, hypersensitivity, or intolerance to AL-335, ODV, or SMV or their excipients (refer to the IBs of AL-335, ODV, and SMV, respectively).
10. Presence of significant co-morbidities, conditions or clinically significant findings during screening of medical history, physical examination, laboratory testing, vital signs or ECG recording for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the safety or well-being) or that

could prevent, limit, or confound the protocol-specified assessments.

11. Organ transplant (other than cornea or hair transplant or skin graft).
12. 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 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 (based on the average of the 3 QTc values);
 - 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 de pointes) or sudden cardiac death.
- 13.1 Any of the following laboratory abnormalities at screening:
 - Platelet count <75 x 10³/μL or <75 x 10⁹/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 10³/μL or <1.00 x 10⁹/L;
 - ALT and/or AST >10 x 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.
14. Other abnormal screening laboratory results that are considered clinically significant by the investigator.

15. 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.

Note: 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.

16. 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 (during treatment and up to 12 weeks after the EOT).
17. 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.
- 18.1 Subject has findings suggestive of hepatocellular carcinoma.
19. Subjects with HCV genotype 3 infection.

NOTE:

- Retesting of laboratory values that lead to exclusion will be allowed once during the screening phase to assess eligibility.
- Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions:

- 1.1 Agree to follow all requirements that must be met during the study as noted in the inclusion (Section 4.1) and exclusion criteria (Section 4.2; eg, contraceptive requirements).
2. Prohibitions and restrictions criterion 2, 3.1, 4, 5, and 6.1 were removed per the HPC2001 protocol amendment 2.

3.1

4.

5.

6.1

7.1 Subjects should be informed that during SMV administration, photosensitivity reactions (rash confined to light-exposed areas), including serious reactions which resulted in hospitalization, have been reported. Photosensitivity reactions occurred most frequently in the first 4 weeks of treatment, but can occur at any time during treatment. Subjects should use sun protective measures (such as a hat, sunglasses, protective clothing, sunscreen) and limit exposure to natural sunlight and avoid artificial sunlight (tanning beds or phototherapy) from baseline until the last intake of SMV. Ideally, outdoor activities should be scheduled outside the hours that ultraviolet radiation is most intense, or should be performed in the shade.

8 Refer to Section [8 PRESTUDY AND CONCOMITANT THERAPY](#) for details regarding prohibited and restricted therapy during the study.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

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

As this is an open study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

Study-site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol (see Section [14.4](#)).

All subjects will receive AL-335, ODV, and SMV at the selected dose for 6 weeks (arm A) or 8 weeks (arm B).

Subjects will receive study drugs in sufficient amounts for 4 weeks of treatment. Provision of study drugs will occur on Day 1 and Week 4 for all subjects. In case of treatment extension to 12 weeks, study drugs will also be dispensed at the Week 8 visit. Subjects will be instructed to continue intake of study drugs exactly up to 6 (43 days) or 8 (57 days) weeks of treatment (or 12 weeks [85 days] in case of treatment extension to 12 weeks), depending on the treatment arm they are in, in order to complete the intended treatment duration. Subjects will be provided with a medication diary to record all dates and times of intake of all study drugs (see Section 7).

For guidance on timing of dosing, dose adjustments and treatment interruptions, see Sections 6.1 and 6.2.

6.1. Timing of Doses

Subjects will attend the study visits and study drugs will be administered as described in the [Time and Events Schedule](#). All subjects should take the study drugs (AL-335, ODV, and SMV) orally, qd and with food, starting on Day 1 after the baseline assessments have been completed (except for the second blood sample for post-dose HCV RNA determination which is to be taken within 4 hours after dosing). Thereafter, all study drugs should be taken together, qd, in the morning at approximately the same time each day with food (ie, during or within 15 minutes after completion of a meal). Study drug intake should take place on site during visits when biochemistry samples are to be taken after fasting for at least 8 hours, and when pre-dose PK sampling is performed (see the [Time and Events Schedule](#) and [Time and Events Schedule: PK Assessments in PK Substudies](#)). At visits where study drug dosing occurs on-site, study sites should have arrangements in place to offer the subjects a meal. Details on the timing of dosing on days with PK blood sampling are presented in the [Time and Events Schedule](#).

The following applies if a scheduled dose of AL-335, ODV, and SMV, is missed:

- If the missed dose is remembered within 12 hours of the scheduled dose time, the dose should be taken as soon as possible.
- If the missed dose is remembered later than 12 hours after the scheduled dose time, the dose should be skipped and the next dose should be taken at the appropriate time.

Note: All missed doses should be recorded in the electronic case report form (eCRF), based on information recorded in medical file after review of the diary and the pill count.

6.2. Dose Adjustment and Treatment Interruption

During the treatment period, dose adjustments of AL-335, ODV, and SMV are not allowed.

The investigator should thoroughly explain to subjects the importance of completing treatment without interruptions. All efforts should be made to keep the subject on treatment for the entire

treatment duration and to avoid any treatment interruptions of study drugs unless deemed necessary due to safety reasons.

Temporary dose interruptions of AL-335, ODV, and SMV will be allowed as long as the interruption is associated with and can be linked to an AE. All efforts must be made to limit the duration of temporary interruptions to not more than 3 consecutive days. The sponsor must be notified when a temporary dose interruption occurs. In the event that AL-335, ODV, or SMV is interrupted (temporarily or permanently), the possibility of continuing treatment with the remaining drug(s) or restarting treatment should be discussed with the sponsor on a case-by-case basis. Subjects should continue with the regular visit schedule during treatment interruption.

Subjects who prematurely discontinue all study drugs will be followed up for 24 weeks after EOT, unless the reason for early treatment discontinuation is withdrawal of consent. Additional unscheduled visits may be performed for safety/tolerability reasons, if needed. Subjects who withdraw consent during the treatment or follow-up phase will be offered an optional safety follow-up visit.

All treatment modifications, interruptions, and discontinuations will be recorded in the eCRF.

6.3. Treatment Stopping Rule (for Viral Breakthrough)

Subjects will discontinue study drugs if the stopping rule is met to limit the risk of developing drug resistance and to reduce unnecessary exposure to study drugs for subjects with no chance or only a small chance of treatment success.

All study drugs will be discontinued for subjects with viral breakthrough defined as a confirmed $>1.0 \log_{10}$ increase in HCV RNA from nadir or confirmed HCV RNA >100 IU/mL in subjects who had previously achieved HCV RNA $<LLOQ$. HCV RNA will be processed in real-time and continuously monitored by the sponsor and communicated to the investigator throughout the study. It is the responsibility of the investigator to monitor the HCV RNA results obtained and ensure that all study drugs are discontinued in subjects with viral breakthrough. Subjects should discontinue treatment as soon as possible once the viral breakthrough criterion is met.

If discontinuation of study drug is necessary, an early treatment withdrawal visit should be scheduled as soon as possible (but no later than 2 weeks) after the HCV RNA results are known by the investigator. In the eCRF, the data will be captured on separate pages (early treatment withdrawal visit pages) and not on the scheduled visit pages.

For details on the assessments during the early treatment withdrawal visit, see the [Time and Events Schedule](#).

Upon review of the HCV RNA data from this study and/or consideration of data from other completed and ongoing studies, including the Phase 2a study AL-335-604, the DRC will make study conduct recommendations, which may include but are not limited to, continuing the study without modifications and/or implementation of treatment prolongation. The sponsor's decision based on the recommendation will be communicated to the investigator.

6.4. Study Treatment Stopping Rules

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 dosing in all subjects in the current study if the event is adjudicated by the DRC to have met the above criteria and 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 72 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. For more information on the reporting of SAEs, see Section [12.3.2](#).

7. TREATMENT COMPLIANCE

The investigator or designated study-site personnel will maintain a log of all provided and returned study drugs. Drug supplies for each subject will be inventoried and accounted for throughout the study (see also Section [14.5](#)).

Subjects will be instructed to bring unused study drugs and empty packaging to the study site at each visit.

Subjects will be provided with a medication diary at the baseline visit to record all dates and times of intake of all study drugs. In addition, on the day of PK assessments and the previous day for PK blood sampling for all subjects and in the sparse PK substudy, it should be recorded if the study drugs were taken with food (ie, during or no later than 15 minutes after a meal). On the day of PK assessments which are part of the rich PK substudy, the start and end times of the meal accompanying the drug intake should be documented; on the previous day it should be recorded if the study drugs were taken with food (ie, during or no later than 15 minutes after a meal). At the baseline visit, study-site personnel will instruct subjects on adherence with study drug administration and on how to correctly complete the medication diary. Subjects will be instructed to return the medication diary at each study visit until the EOT. Study-site personnel is to review the medication diary for adherence and perform adherence counseling at each on-treatment study visit. Given the short treatment duration, the investigator should discuss the importance of treatment adherence with the subject at every visit and, in case study drug intake is not according to the protocol, try to identify and address factors that may negatively impact adherence and, if applicable, notify the sponsor (see Section [6.2](#)).

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy therapies (prescriptions or over-the-counter medications, including vitamins and herbal supplements, nonpharmacologic therapies such as electrical stimulation, acupuncture, special diets, or exercise regimens) administered within 30 days before the start of screening must be recorded at screening. Consumption of large quantities of grapefruit juice (>1 liter/day) is disallowed from baseline till EOT.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) used during the study different from the study drug (AL-335, ODV, and SMV) must be recorded in the eCRF. Recorded information will include a description of the type of drug, treatment period, dosing regimen, route of administration, and its indication. Patients on disallowed medication (see [Table 1](#)) are excluded from the study. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a subject into the study.

For study-specific rules on the use of contraceptive methods, refer to [Section 4.3](#).

AL-335 is metabolized by esterases and is not a substrate of any CYP enzymes. AL-335 (and the metabolites ALS-022399 and ALS-022227) has demonstrated a very low inhibition potential to CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A. AL-335 is a substrate for P-gp but does not inhibit P-gp. Co-administration of AL-335 with inhibitors of P-gp may increase AL-335 plasma concentrations. ALS-022399 and ALS-022227 are neither substrates nor inhibitors of P-gp, OATP1B1, OATP1B3, OAT1, OAT3 or OCT2 transport.

ODV has demonstrated a low inhibition potential for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A. ODV is primarily cleared by biliary secretion, is not significantly metabolized, and is not expected to be involved with clinically significant DDIs associated with the CYP enzyme system. ODV is neither a substrate nor an inhibitor of transporters such as OATP1B3, BCRP, MRP2, MRP3, and BSEP. ODV is a low-affinity substrate of OATP1B1 and does not inhibit OATP1B1. ODV is not a substrate but is an inhibitor of P-gp. Co-administration of ODV with drugs that are substrates for P-gp transport may result in increased plasma concentrations of such drugs.

SMV is a mild inhibitor of intestinal CYP3A. Co-administration of SMV with drugs that are primarily metabolized by CYP3A may result in mild increases in plasma concentrations of such drugs, which could increase or prolong therapeutic effect and adverse reactions of CYP3A substrates with narrow therapeutic index. Drugs that induce CYP3A may decrease SMV plasma concentrations and reduce the therapeutic effect of SMV. Co-administration of SMV with inhibitors of CYP3A may increase SMV plasma concentrations. Clinically, SMV inhibits uptake transporters OATP1B1/3 and the efflux transporters P-gp/multidrug resistance protein 1 and MRP2. Co-administration of SMV with drugs that are substrates for OATP1B1/3, and P-gp transport may result in increased plasma concentrations of such drugs.

An overview of disallowed concomitant medication is presented in [Table 1](#). An overview of concomitant medication that should be used with caution follows after the table.

Table 1: Disallowed Medication

Disallowed at any time prior to screening and during the study period, including post treatment follow-up:

- Previous treatment with any approved or investigational anti-HCV drug (including vaccines) other than (Peg)IFN/RBV.

Note: Prior hepatic treatment with herbal or nutritional products is allowed but should be stopped at screening

Disallowed within 30 days of screening, during screening and during the entire treatment period:

- All non-HCV investigational drugs or invasive investigational medical devices.
- Experimental non-HCV vaccines.

Note: Approved non-HCV vaccines are allowed

Disallowed within 3 months prior to screening until the end of the study:

- The antiarrhythmic amiodarone.

Disallowed from screening onwards until the EOT:

- Immunomodulators (eg, cyclosporine, interleukins, or systemic corticosteroids in immunosuppressive dose).
- Any herbal or nutritional products for HCV treatment including silibinin, silybin, silymarin (milk thistle).
- Antiarrhythmics: disopyramide, flecainide, mexiletine, systemic lidocaine, propafenone, quinidine.
- Beta-blockers.
- Proton-pump inhibitors (eg, [dex]lansoprazole, [es]omeprazole, rabeprazole).

Disallowed from screening onwards until the end of the study

- Ca-channel blockers (eg, amlodipine, bepridil, diltiazem, felodipine, nifedipine, nisoldipine, verapamil, nicardipine).
- Na-channel blockers (eg, disopyramide, flecainide, lidocaine, mexiletine, moricizine, procainamide, propafenone, quinidine, tocainide)
- K-channel blockers (eg, bretylium, dronedarone, sotalol, ibutilide, dofetilide)

Disallowed from 2 weeks before baseline and during the treatment period:

- Potent and moderate CYP3A4 inducers, such as:
 - The anti-epileptics: carbamazepine, oxcarbazepine, (fos)phenytoin, phenobarbital.
 - The anti-tuberculosis drugs: rifabutin, rifampin, and rifapentine.
 - Systemic dexamethasone (if more than a single dose).
 - Miscellaneous: products containing *Hypericum perforatum* (St. John's Wort).
- P-gp inhibitors (eg, clarithromycin, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, quinidine, ritonavir, verapamil).

Disallowed from baseline onwards until the EOT:

- Potent and moderate CYP3A4 inhibitors, such as:
 - The antifungals (systemic): ketoconazole, itraconazole, voriconazole.
 - The antibiotics (systemic): clarithromycin, erythromycin, troleandomycin, and telithromycin.
 - The antiretrovirals: (fos)amprenavir, atazanavir, delavirdine, darunavir, efavirenz, etravirine, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, tipranavir.
 - Miscellaneous: cobicistat-containing products.
- CYP3A substrates with narrow therapeutic index, eg:
 - Antihistamines astemizole and terfenadine.
 - Gastrointestinal/gastroesophageal reflux disease drugs: cisapride.

Disallowed from 14 days before baseline until W4 FU:

- Oral contraceptives.

Notes:

- The list of disallowed concomitant medication is not exhaustive; for drugs falling in one of the categories defined by respective CYP or P-gp interaction and not mentioned by name, the sponsor should be contacted to determine whether the drug can be allowed.
- As sacubitril can interfere with BNP measurement, sacubitril-containing products are disallowed from screening until W4 FU.

In addition to the disallowed medications outlined in [Table 1](#), drugs which are known to prolong the QTc interval (refer to the list of drugs provided by the Arizona Center for Education and Research on Therapeutics³⁷) may not be newly initiated once a subject has begun study drug treatment unless the medication is necessary to protect subject safety and it has been discussed with the sponsor. An ECG should be performed prior to initiating any drugs which may prolong the QTc interval. Drugs which prolong the QTc (eg, methadone, citalopram) are permitted as prior/concomitant medications if they have been administered chronically with an unchanged dose (at least 2 months prior to screening) and the subject's QTc interval is normal (see in- and exclusion criteria in [Section 4](#)).

An overview of concomitant medication that should be used with caution is presented in [Table 2](#).

Table 2: Concomitant Medication to be Used With Caution

The following concomitant medication is allowed, but should be used with caution and be started at the lowest possible dose, with monitoring of AEs and desired efficacy

- Analgesics: ergaloid mesylates, ergotamine tartrate, dihydroergotamine and methylergonovine.
 - Lipid-lowering drugs: atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin.
 - Phosphodiesterase 5 inhibitors: sildenafil, tadalafil.
 - Sedatives/anxiolytics: midazolam, triazolam.
 - Acid-reducing agents: antacids (eg, aluminium and magnesium hydroxide) (recommended to separate antacid and study drug administration by 4 hours), H2-receptor antagonists (eg, ranitidine) (may be administered simultaneously with or 12 hours apart from study drugs).
-

The manufacturer's prescribing information for SMV and the IB of AL-335 and ODV may be consulted for additional details on drug-interaction potential.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition must be documented in the AE section of the eCRF.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The [Time and Events Schedule](#) summarizes the frequency and timing of all measurements and evaluations applicable to this study.

All visit-specific PRO assessments should be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject's perceptions.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For all subjects, less than 500 mL of blood will be drawn during each 60-day interval throughout the study, which is within the limits of standard blood donation.

The first screening assessment has to be performed within 6 weeks prior to the baseline visit (ie, Day 1). The timing of visits during the treatment phase should be based on the start date of study drug intake (ie, at the baseline visit on Day 1). The subject should be encouraged to come within the following time windows:

- For visits on Days 2 and 3: no time window allowed.
- For visit at Week 1 of the treatment phase: -1 to +1 day.
- For visits at Weeks 2 and 3 of the treatment phase: -2 to +2 days.
- For visits at Weeks 4, 6, 8 and 10 and 12 (if applicable) of the treatment phase: -2 to +2 days (only applicable when the respective visits are not the EOT visit)
- For the EOT visit: no time window allowed.
- For visit at W4 FU: -3 to +3 days.
- For all other scheduled visits during the 24-week follow-up phase: -7 to +7 days. These time windows may be shortened when approaching a data analysis. If this is the case, sites will be informed.

9.1.2. Screening Phase

Within 6 weeks prior to the baseline visit and after signing and dating the ICF, the first screening assessment should be performed. Screening assessment as indicated in the [Time and Events Schedule](#) may be split over more than one visit.

A complete physical examination (including body weight, height and body systems and, if considered necessary by the investigator based on the subject's past and present medical history, breast, genitals or rectal examination) will be conducted and the following will be recorded for each subject: demographics, medical and surgical history, concomitant disease, and prestudy therapies and vital signs.

Echocardiography and triplicate ECG will be performed at screening. Electrocardiogram and echocardiography findings will be recorded for each subject.

Blood sampling for determination of the HCV geno/subtype and HCV RNA level will be performed. In addition, a blood sample for hematology and biochemistry, and a urine sample for urinalysis (including a urine drug screening test) will be collected. Hepatitis A, B and C serologic testing, and HIV-1 and HIV-2 serologic testing will also be performed.

A serum pregnancy test will be performed in women of childbearing potential. The FSH level will be tested in female subjects who are postmenopausal for less than 2 years, for whom the date of last menses will be recorded in the eCRF.

Absence of cirrhosis will be determined by the methods described in Section 4.1.

Occurrence of clinical events related to AEs and pregnancies will be reported from the time a signed ICF is obtained.

The investigator will assess the overall eligibility of the subject to participate in the study once all screening values and results of any other required evaluations are available and document this in the source documents. Retesting of values (eg, safety laboratory or HCV RNA) that lead to exclusion will be allowed once using an unscheduled visit during the screening phase to assess eligibility. In exceptional cases, the screening phase can be extended if discussed with and approved (documented) by the sponsor, eg, if not all the test results become available during the allocated 6 weeks; this will be evaluated on a case-by-case basis.

9.1.3. Open-label Treatment Phase

If eligible, subjects to be enrolled in the study will be randomly assigned in a 1:1 ratio to treatment arms A or B and all subjects will come for the baseline visit. Investigators should ensure that all study enrollment criteria have been met during screening. If, after screening but prior to the first dose of study drugs, a subject's clinical status (including any available laboratory results or receipt of additional medical records) changes such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study.

Information on drug dosage and administration is provided in Section 6, and information on the use of the medication diary is provided in Section 7.

All baseline assessments need to be performed before study drug intake, except for the second blood sample on Day 1 for HCV RNA determination, which should be taken post-dose but within 4 hours after dosing. The time when the pre- and post-dose blood sample is obtained as well as the timing of the baseline dosing should be recorded in the eCRF.

From the baseline visit onwards, at sites where appropriate translations are available, PRO assessments (CLDQ-HCV, EQ-5D-5L, FSS, and SF-36v2) are to be completed before any tests, procedures or other consultations for that visit, and at the time points indicated in the [Time and Events Schedule](#).

MRU data will be collected at all scheduled visits.

A pharmacogenomic blood sample for host *IL28B* genotyping and, where locally permitted, and upon consent of the subject (in addition to the consent for the main part of the study) an optional additional blood sample will be collected at baseline for exploratory host DNA research related to AL-335 (and metabolites), ODV, and SMV, and limited to genes involved in the metabolism of the study drugs as well as drug transporter genes.

Targeted physical examinations (ie, physical examinations directed at specific body systems as required based on the clinical presentation) (including body weight), vital sign measurements and blood and urine sampling for clinical laboratory assessments will be performed at the time points indicated in the [Time and Events Schedule](#).

For female subjects of childbearing potential, a urine pregnancy test will be performed on Day 1 and at least every 4 to 6 weeks up to the W24 FU visit as indicated in the [Time and Events Schedule](#).

Blood sampling for determination of the HCV RNA level (2 samples taken on Day 1; 1 pre-dose and 1 post-dose but within 4 hours after dosing) and for viral sequencing will be performed at all scheduled visits. Viral sequencing will be performed on pre-treatment (baseline) samples of all subjects by default and on post-baseline samples of subjects not achieving SVR. Sequencing of additional samples may be triggered by the sponsor's virologist. A retest sample for confirmation of the HCV RNA result will be needed in case viral breakthrough is suspected. At the time of the retest sample for HCV RNA, a sample for viral sequencing will also be collected.

Occurrence of clinical events related to all AEs, whether serious or non-serious, pregnancies and use of concomitant medication will be reported throughout the treatment phase.

Echocardiography and triplicate ECG (central reading) will be performed at the time points indicated in the [Time and Events Schedule](#). Additional ECG, echocardiography or cardiac monitoring may be done at any time during the study if clinically indicated in the opinion of the investigator.

Pharmacokinetic blood samples to determine the plasma concentrations of AL-335 (and metabolites), ODV, and SMV will be collected at any time during the visit for all subjects at the Week 4 visit, the Week 6 visit (arm B) and at the EOT visit. At the EOT visit, subjects should still be on treatment at the time of the PK assessment. In addition, at selected sites, a rich PK substudy and a sparse PK substudy will be performed in subsets of subjects (ie, 20 subjects each for the rich PK substudy and sparse PK substudy) as indicated in the [Time and Events Schedule: PK Assessments in PK Substudies](#). For PK sampling in the sparse PK substudy, at least 5 subjects are to be included from each treatment arm.

From baseline onwards, subjects' occupational/employment status will be checked throughout the treatment phase as indicated in the [Time and Events Schedule](#).

In case a treatment extension is recommended by the DRC, treatment duration of the arms will be extended up to a maximum of 12 weeks (ie, the 6-week arm will be extended to 8 weeks, or both arms will be extended to 12 weeks). All subjects will continue to attend study visits every 2 weeks. In case of treatment extension to 8 weeks, the subjects should follow the visit schedule of subjects initially included in the 8-week treatment arm, with an EOT visit at Week 8. In case of treatment extension to 12 weeks, subjects should follow the schedule for the 12-week treatment extension arm with an EOT visit at Week 12.

If study drug treatment is discontinued prematurely, for reasons other than withdrawal of consent, a treatment withdrawal visit should be scheduled as soon as possible after the EOT. The subjects will be followed-up for 24 weeks after EOT, with visits as indicated in the [Time and Events Schedule](#). If a subject discontinues treatment due to withdrawal of consent, the subject will be offered an optional early treatment withdrawal visit, to be scheduled as soon as possible after withdrawal and/or a safety follow-up visit, which needs to be scheduled 4 weeks after EOT. At the safety follow-up visit safety assessments of the W4 FU visit need to be performed.

9.1.4. Post-treatment Phase (Follow-Up)

All subjects will enter the 24-week follow-up phase, except for subjects who withdraw consent. The latter subjects will be offered an optional safety follow-up visit, at which the assessments of the W4 FU visit need to be performed. If applicable, PRO assessments (CLDQ-HCV, EQ-5D-5L, FSS, and SF-36v2) are to be completed at visits as indicated in the [Time and Events Schedule](#) before any tests, procedures or other consultations for that visit.

Any subject who withdraws consent during the follow-up phase and/or notifies the site he or she will not return for study visits, will be invited to do a follow-up visit at the time of withdrawal to complete the full set of protocol procedures as scheduled for the W24 FU visit. However, all possible efforts should be made to ensure that subjects complete the study.

Patient-reported outcomes assessments (CLDQ-HCV, EQ-5D-5L, FSS, and SF-36v2) are to be completed before any tests, procedures or other consultations for that visit at the time points indicated in the [Time and Events Schedule](#).

MRU data will be collected at all scheduled visits.

Targeted physical examinations (including body weight) and vital sign measurements will be performed at the W4 FU and W24 FU visit.

Subjects' occupational/employment status will be checked at each of the follow-up visits.

Echocardiography and triplicate ECG will be performed at the W4 FU visit.

Blood and urine samples for clinical laboratory assessments and a urine pregnancy test will be performed at the time points indicated in the [Time and Events Schedule](#).

Blood samples for PK assessment of ODV will be collected, in approximately 20 subjects who are participating to the sparse PK substudy, at the time points indicated in the [Time and Events Schedule: PK Assessments in PK Substudies](#).

Blood sampling for determination of the HCV RNA level and for viral sequencing will be performed at all scheduled visits.

During follow-up, suspected relapse, ie, HCV RNA \geq LLOQ after previous $<$ LLOQ, needs to be confirmed preferably within 2 weeks after the result has become available, and this retest may

require an unscheduled visit which should be scheduled by the investigator. At the time of the retest sample for HCV RNA, a sample for viral sequencing will also be collected.

All AEs, whether serious or non-serious, and pregnancies will be reported until the subject's last study visit. The use of concomitant medication will be reported throughout the follow-up phase.

9.2. Efficacy

9.2.1. Evaluations

9.2.1.1. HCV RNA Levels

Blood samples for the determination of HCV RNA levels will be taken at all scheduled visits, processed in real time and results closely monitored by the sponsor. Determination of HCV RNA levels will be performed by a central laboratory contracted by the sponsor. Plasma HCV RNA levels will be determined using an in vitro nucleic acid amplification test for quantification of HCV RNA in human plasma. The procedures for sample collection, processing and storage will be provided in the laboratory manual.

On Day 1, 2 blood samples should be taken: the first one pre-dose and the second one post-dose but within 4 hours after dosing. The time when the pre- and post-dose blood sample is obtained as well as the timing of the dosing at baseline should be recorded in the eCRF.

Results of the HCV RNA measurements will be communicated to the investigator and the sponsor. It is the responsibility of the investigator to monitor the HCV RNA results obtained and ensure that all study drugs are discontinued in subjects with viral breakthrough (please see Section 6.3, Treatment Stopping Rule [for Viral Breakthrough]).

During follow-up, suspected relapse, ie, HCV RNA \geq LLOQ after previous $<$ LLOQ, needs to be confirmed preferably within 2 weeks after the result has become available, and this retest may require an unscheduled visit which should be scheduled by the investigator.

Changes in HCV RNA levels will not be reported as AEs or SAEs.

9.2.1.2. Alanine Aminotransferase and Aspartate Aminotransferase

Alanine aminotransferase and AST levels will be determined as part of the biochemistry panel of the clinical laboratory tests (see Section 9.8.2). Samples for biochemistry will be taken at the time points indicated in the [Time and Events Schedule](#) and will be processed in real time.

9.2.1.3. Resistance Determinations

Sequencing of the HCV NS3/4A, NS5A and NS5B regions will be performed to identify pre-existing sequence polymorphisms and characterize emerging HCV variants.

Samples for viral sequencing will be taken at all scheduled visits except at screening.

The NS3/4A, NS5A and NS5B regions will be sequenced pre-treatment (at baseline) by default in all subjects and post-baseline in subjects not achieving SVR. Sequencing of additional samples may be triggered by the sponsor virologist.

Changes in viral genotype will be evaluated by the sponsor virologist. They will not be reported as AEs or SAEs.

Additional exploratory characterization of the viral genotype and phenotype may be performed. No human DNA analysis will be performed on these samples.

9.2.1.4. Patient-reported Outcomes

The impact of HCV and its treatment (safety and efficacy) on patient-reported symptoms, functioning and HRQoL will be evaluated at the time points indicated in the [Time and Events Schedule](#), using the PRO assessments CLDQ-HCV, EQ-5D-5L, FSS, and SF-36v2. Patient-reported outcomes assessments will be performed by all subjects at sites where appropriate translations are available. Subjects should complete these assessments in their native language or if there is no version available in their native language, a version in a language in which the subject is fluent and literate. It is preferable that subjects are able to read and write to complete the assessments by themselves. If a subject is unable to read or has visual or other physical limitations that make it difficult to read or complete the assessments, trained study-site personnel may read the questions and responses aloud exactly as they appear on the assessment and record the subject's responses.

Study-site personnel will instruct subjects how to self-administer the PRO tools and will record in the eCRF whether the PRO assessments were performed during the study visit.

Subjects will complete the PRO assessments electronically during study site visits on a touch-screen tablet provided for this study. The subject should be provided a quiet place to complete the PRO assessments, and instructed how to complete the PRO assessment on the tablet. When deciding which answer to report, subjects should not receive any help from anyone accompanying them (such as family members and friends) or study-site personnel; the responses should reflect the subject's interpretation and response.

Subjects' responses to the PRO questionnaires will not be reported as AEs or SAEs.

Chronic Liver Disease Quality of Life Questionnaire

The CLDQ-HCV questionnaire is a fully validated disease-specific HRQoL instrument to assess health-related quality of life in patients with chronic hepatitis C. The questionnaire is supposed to capture HRQoL impairments such as (fatigue, activity, emotional function, abdominal symptoms, systemic symptoms and worry). CLDQ-HCV includes four HRQoL domains: activity and energy (AE), emotional (EM), worry (WO), and systemic (SY). There are domain scores and a total CLDQ-HCV score which ranges from 1 to 7 with higher values representing better HRQoL. The answers to each of the questions are from 1-7 on a Likert scale which are then averaged to the total CLDQ total score. The CLDQ-HCV questionnaire is comprised of

29 questions which is short, easy to administer and produces both a summary score and domain scores.

It takes 10 minutes to complete the CLDQ-HCV questionnaire. See [Attachment 3](#) for a representative example of the CLDQ-HCV questionnaire.

Health Status and Quality of Life

The EQ-5D-5L questionnaire is a brief, 2-page, generic HRQoL assessment that evaluates a subject's self-rated health state on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Additionally, a VAS records the subject's self-rated health on a vertical VAS where the endpoints are labelled 'best imaginable health state' (100) and 'worst imaginable health state' (0). This information can be used as a quantitative measure of health outcome as judged by the subject. EQ-5D scores include the following:

- EQ-5D Valuation Index (VI) score (a weighted scoring of the 5 dimension scores with a possible range from 0 to 1);
- EQ-5D VAS score (with a possible range from 0 [worst imaginable health] to 100 [best imaginable health]);
- EQ-5D descriptive system scores (5 scores reflecting each of the 5 dimensions ranging from 0 [no limitation] to 4 [incapacity]).

It takes 5 minutes to complete the EQ-5D-5L questionnaire. See [Attachment 4](#) for a representative example of the EQ-5D-5L.

Fatigue Severity Scale

The FSS is a questionnaire with 9 items developed to assess the impact of fatigue on subjects and has been used extensively in studies of chronic HCV infection in which it has shown good internal consistency, test-retest reliability, and content and construct validity.²⁰ Item responses are measured on a 7-point Likert scale ranging from strongly disagree (1 point) to strongly agree (7 points). The 9 items are averaged to produce a total score; a lower total score indicates less effect of fatigue on everyday life. The recall period of the FSS used in this study is 2 weeks (the past 14 days). It takes 5 minutes to complete the FSS questionnaire. See [Attachment 5](#) for a representative example of the FSS.

SF-36v2

SF-36v2 is a generic 36-item questionnaire measuring HRQoL that can be interpreted using 2 summary scores – PCS and MCS – as well as domain subscales. The SF-36v2 consists of 8 subscales. Although SF-36v2 PCS and MCS scores include information from all 8 SF-36 domains, the PCS score gives more weight to physical aspects of HRQoL as represented in the Physical functioning, Physical role limitations, Pain, and General health perception domain scores. The MCS score gives more weight to the emotional and social aspects of HRQoL as assessed by the Vitality, Social function, Social role limitations, and Mental health domain

scores. Participants self-report on items in a subscale that have between 2-6 choices per item using Likert-type responses (eg, none of the time, some of the time, etc.). Summations of item scores of the same subscale give the subscale scores, which are transformed into a range from 0 to 100; 0=worst HRQoL, 100=best HRQoL. Physical component summary and MCS scores are constructed as a T-score with a mean of 50 and standard deviation of 10 and no minimum or maximum score; higher scores indicate better health status.

It takes 5 minutes to complete the SF-36v2 questionnaire. See [Attachment 6](#) for a representative example of the SF-36v2.

9.2.2. Endpoints

9.2.2.1. Primary Endpoints

The primary efficacy endpoint is:

- The proportion of chronic HCV infected subjects who achieve SVR12.

For the definition of SVR12, see the [Definitions of Terms](#).

9.2.2.2. Secondary Endpoints

The secondary efficacy endpoints are:

- The proportion of subjects with SVR4 and SVR24,
- The proportion of subjects with viral relapse,
- The proportion of subjects with on-treatment failure,
- The proportion of subjects with virologic response:
 - HCV RNA <LLOQ undetectable,
 - HCV RNA <LLOQ,
- Time to achieve undetectable HCV RNA and HCV RNA <LLOQ,
- The effect of the presence or absence at baseline of NS5A, NS5B or NS3/4A polymorphisms on treatment outcome,
- The changes from baseline in amino acid sequence in the HCV NS3/4A, NS5A and NS5B regions in subjects not achieving SVR,
- The relationship between the population-derived exposure parameters of SMV (AUC_{24h} and C_{0h}) with SVR12 and safety,
- Change from baseline over time in mean score for each of the following PRO scores:
 - EQ-5D-5L: VAS score,
 - FSS: Total score,
- The proportion of subjects with clinically important improvement from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in FSS total and EQ-5D-5L VAS scores,

- The time to clinically important improvement from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in FSS total and EQ-5D-5L VAS,
- The proportion of subjects with clinically important worsening from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in FSS total and EQ-5D-5L VAS,
- The duration (weeks) of clinically important worsening from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in FSS total and EQ-5D-5L VAS,
- Change from baseline over time in EQ-5D-5L VI score and Domain scores.

For definitions of on-treatment virologic response, SVR4, SVR24, on-treatment failure and viral relapse, see the [Definitions of Terms](#).

9.2.2.3. Exploratory Endpoints

The exploratory efficacy endpoints are:

- Change from baseline over time in mean score for each of the following PRO scores:
 - SF-36v2 PCS and MCS scores,
 - CLDQ-HCV summary and domain scores,
- The proportion of subjects with clinically important improvement from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in each of the PRO scores mentioned above,
- The time to clinically important improvement from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in each of the PRO scores mentioned above,
- The proportion of subjects with clinically important worsening from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in each of the PRO scores mentioned above,
- The duration (weeks) of clinically important worsening from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24 in each of the PRO scores mentioned above,
- Change from baseline over time in EQ-5D-5L Domain scores,
- The effect of prior HCV treatment history, baseline host and disease related characteristics including but not limited to HCV geno/subtype, baseline HCV RNA level, genetic factors (eg, *IL28B*, the presence of NS3/4A, NS5A and NS5B polymorphisms), race, sex and age on treatment outcome.

9.3. Pharmacokinetics

9.3.1. Evaluations

Blood samples for PK assessments of AL-335 (and metabolites), 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. At the EOT visit, subjects should still be on treatment at the time of the PK assessment (the last dose is expected to be taken on the morning of the visit).

The following times need to be recorded in the eCRF: date and time of study drug intake on the day of the PK blood sampling and the previous day, and date and time of PK blood sampling; it will be recorded whether study drugs were taken with food (ie, during or no later than 15 minutes after a meal) on the day of PK blood sampling and on the previous day. For details on study drug intake, see Section 6.

Rich Serial PK Substudy

In the **rich serial PK substudy**, performed at selected study sites, rich serial PK blood sampling for the measurement of plasma concentrations of AL-335 (and metabolites), ODV, and SMV will be performed in approximately 20 subjects (arms A and B combined).

Subjects participating in the rich serial PK substudy will undergo rich serial PK sampling at their Week 4 visit, at 10 different time points within the dosing interval. The first sample should be collected before study drug intake (within 0.5 hour before). Thereafter, study drugs (AL-335, ODV, and SMV) will be administered with a standardized breakfast. Samples 2 to 10 should be collected at 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours after study drug intake. No additional sample is needed to cover the PK sample to be taken at any time during the visit at Week 4. This sampling schedule may require an overnight stay and the 24-hour PK sample must be taken before study drug intake on the morning following the overnight stay. Subjects participating in the rich serial PK substudy will not participate in the sparse PK substudy.

A standardized breakfast will consist of (or its equivalent) 4 slices of bread, 2 slices of ham and/or cheese, butter, jelly, and 2 cups (up to 480 mL) of decaffeinated coffee or decaffeinated tea with milk and/or sugar, if desired (containing approx.: fat, 21 g; carbohydrates, 67 g; proteins, 19 g; calories, 533) and should be eaten completely within 30 minutes. The study drugs should be taken during or no later than 15 minutes after completing the breakfast.

The following times need to be recorded in the eCRF: actual dates and times of study drug intake on the day of the visit and the previous and the next day and actual dates and times of PK blood sampling. In addition, start and end times of accompanying meal on the day of the PK sampling need to be recorded and it should be documented whether subjects took their study drugs in fed state (during or within 15 minutes after completion of a meal) on the day prior to the visit. For details on study drug intake, see Section 6.

Sparse PK Substudy

In the sparse PK substudy, at selected sites, sparse PK sampling for AL-335 (and metabolites), ODV, and SMV will be performed for a subset of approximately 20 subjects (arms A and B combined) who are not participating in the rich serial PK substudy.

At least 5 subjects are to be included from each arm.

Blood samples will be collected at the following time points (see also [Time and Events Schedule: PK Assessments in PK Substudies](#)):

- At the Week 2 visit: pre-dose and 2-4 hours post-dose,
- After 6 weeks of treatment (ie, EOT visit [arm A] and Week 6 visit [arm B]): 6-12 hours post-dose,

Note: for subjects in the sparse PK substudy, this sample replaces the PK sample to be taken at any time during the visit at the EOT visit (arm A) and at the Week 6 visit (arm B).

- After 8 weeks of treatment (ie, EOT visit [arm B]): pre-dose and 2-4 hours post-dose,
- At W4 FU, W12 FU, and W24 FU: for ODV only, any time during the visit.

At the EOT visit, subjects should still be on treatment at time of the PK assessment (the last dose is expected to be taken on the morning of the visit). In case of treatment extension to 8 weeks or 12 weeks, no additional PK assessments will be done.

The following times need to be recorded in the eCRF: date and time of study drug intake on the day of the PK blood sampling and the previous day, and date and time of PK blood sampling; it will be recorded whether study drugs were taken with food (ie, during or no later than 15 minutes after a meal) on the day of PK blood sampling and on the previous day. For details on study drug intake, see Section 6.

9.3.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of AL-335 and its metabolites ALS-022227 and ALS-022399, ODV, and SMV using validated, specific, and sensitive methods (eg, liquid chromatography-mass spectrometry/mass spectrometry) by or under the supervision of the sponsor.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites or to determine protein binding using a qualified research method.

9.3.3. Pharmacokinetic Parameters

Based on the individual plasma concentration-time data from all subjects (including those of subjects in the PK substudies), exposure parameters of AL-335 and its metabolites ALS-022227 and ALS-022399, ODV, and SMV will be derived using population PK (popPK) modeling. Potential baseline covariates (eg, demographics such as age, sex and race, body weight, laboratory variables such as creatinine clearance, genotype, etc.) may be included in the models, if relevant. The following exposure parameters for AL-335 (and metabolites), ODV, and SMV will be derived using Bayesian feedback analysis: AUC_{24h} and C_{0h} .

Rich serial PK sampling

For subjects participating in the rich serial PK substudy, the following PK parameters for AL-335 (and metabolites), ODV, and SMV will be derived using non-compartmental methods: C_{0h} , C_{max} , t_{max} , C_{min} , and AUC_{24h} .

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

Relationships of AL-335 (and metabolites), ODV, and SMV population-derived exposure parameters (C_{0h} and AUC_{24h}) with SVR12 and with safety endpoints will be graphically explored.

9.5. Pharmacogenomic (DNA) Evaluations

9.5.1. Genotyping of *IL28B*

One mandatory blood sample for host *IL28B* genotyping will be collected at the baseline visit, providing the opportunity to explore the influence of a genetic polymorphism upstream of the *IL28B* gene (rs12979860) on treatment outcome to the drug regimen assessed in this study. Determination of the subject's *IL28B* genotype will be performed on human genomic DNA by techniques allowing amplification of the DNA and identification of the polymorphism.

9.5.2. Genotyping for Drug Metabolism and Transporter Genes

Where locally permitted and upon consent of the subject (in addition to the consent for the main part of the study), an additional optional blood sample will be collected for all subjects at the baseline visit for exploratory host DNA research related to AL-335, ODV, and SMV, providing the opportunity to explore the genetic basis of host factors that influence response to therapy, PK and side effects. Only genes involved in the metabolism of the study drugs (eg, *CYP2C19* and *CYP3A5*), as well as drug transporter genes (eg, *OATP1B1*, *ABCG2*, *ABCB1*, and *MRP2*) may be analyzed to potentially help in assessing the relationship between variants in these genes and drug efficacy, safety, and PK.

Both blood samples for pharmacogenomic evaluations will preferably be collected at the baseline visit. However, if necessary eg, in case of a technical failure, they may be collected at a later time point without constituting a protocol deviation.

9.6. Occupational/Employment Status

Occupational/employment status will be collected in the eCRF by the investigator and study-site personnel for all subjects at the time points indicated in the [Time and Events Schedule](#).

9.7. Medical Resource Utilization

MRU data, associated with medical encounters, will be collected in the eCRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded from MRU data collection. The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient),
- Duration of hospitalization (total days length of stay, including duration by wards; eg, intensive care unit),
- Number and character of diagnostic and therapeutic tests and procedures,
- Outpatient medical encounters and treatments (including physician or emergency room visits, tests and procedures, and medications).

9.8. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the AE Section of the eCRF.

All AEs, whether serious or non-serious and pregnancies, will be reported from the time a signed ICF is obtained until the subject's last study visit. The use of concomitant medication will be reported throughout the study period.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Anticipated events will be recorded and reported as described in [Attachment 8](#).

The study will include the following evaluations of safety and tolerability according to the time points provided in the [Time and Events Schedule](#).

9.8.1. Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12.

9.8.2. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected. The investigator must review the laboratory report, document this review, and record in the Adverse Event Section of the eCRF any clinically relevant changes, occurring from signing of the ICF onwards until the subject's last study visit. The laboratory reports must be filed with the source documents.

Biochemistry samples on Day 1, Week 2, Week 4, EOT, W4 FU, and W12 FU must be taken after fasting for at least 8 hours. The lipid profile is to be assessed at these visits, ie, after fasting.

The following tests will be performed by the selected central laboratory:

- Hematology Panel

- | | |
|---|---------------------------------|
| - hemoglobin | - WBC differential ^b |
| - hematocrit | - neutrophils |
| - red blood cell (RBC) count ^a | - lymphocytes |
| - RBC parameters ^a : | - monocytes |
| - mean corpuscular hemoglobin | - eosinophils |
| - mean corpuscular hemoglobin concentration | - basophils |
| - mean corpuscular volume | - platelet count |
| - white blood cell (WBC) count ^b | |

^a RBC evaluation may include abnormalities in RBC count and/or RBC parameters and/or RBC morphology, which will then be reported by the laboratory.

^b WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.

The samples will also be used for coagulation tests. Prothrombin time and activated partial thromboplastin time will be assessed, and the International Normalized Ratio will be calculated. In addition, the hematology sample taken at screening will include testing for glycosylated hemoglobin.

- Serum Chemistry Panel

- | | |
|--|--|
| - sodium | - alpha-1 acid glycoprotein |
| - potassium | - lipase |
| - chloride | - CK |
| - creatinine | - lactate dehydrogenase |
| - blood urea nitrogen | - uric acid |
| - glucose ^a | - calcium (corrected for albumin) |
| - AST | - phosphate |
| - ALT | - serum albumin |
| - gamma-glutamyltransferase | - total protein |
| - total, direct, indirect bilirubin | - total cholesterol |
| - insulin ^a | - high-density lipoprotein cholesterol |
| - pancreatic amylase | - low-density lipoprotein cholesterol |
| - alkaline phosphatase | - triglycerides |
| - thyroid stimulating hormone (TSH) ^b | - creatinine clearance |
| - BNP ^c | |

^a The homeostasis model assessment insulin resistance (HOMA-IR) index will be derived from plasma insulin and plasma glucose (fasting) test results performed on the biochemistry sample taken after fasting at baseline, EOT and W12 FU.

^b TSH is to be assessed at screening and EOT or early withdrawal. In case TSH is not within the normal range, testing of fT3 and fT4 will be performed.

^c BNP is to be assessed at baseline, Week 2, Week 4, Week 6, EOT and W4 FU.

For each time point of the laboratory assessments, the selected central laboratory will also estimate the GFR according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.²⁴

- Urinalysis

- Dipstick

- specific gravity
 - pH
 - glucose
 - protein
 - blood
 - ketones
 - bilirubin
 - urobilinogen
 - nitrite
 - leukocyte esterase

- Sediment (if dipstick result is abnormal)

- RBCs
 - WBCs
 - epithelial cells
 - crystals
 - casts
 - bacteria

If dipstick result is abnormal, microscopy will be used to examine sediment. In the microscopic examination, observations other than the presence of WBCs, RBCs and casts may also be reported by the laboratory.

- Serum pregnancy testing will be performed at screening for women of childbearing potential. Urine pregnancy testing will be performed for women of childbearing potential only at the time points indicated in the [Time and Events Schedule](#). The results of the pregnancy test should be recorded in the eCRF and in the subject's medical record.
- FSH will be tested at screening for female subjects who are postmenopausal for less than 2 years.
- Serology (HIV-1 and HIV-2 antibody, hepatitis A immunoglobulin M antibody, hepatitis B surface antigen, hepatitis C antibody) will be performed at screening. Routine antibody testing will be performed to evaluate HIV infection status and additional testing will be done whenever clinically relevant.
- An additional sample for anti-HBc testing will be taken at baseline. For anti-HBc positive subjects anti-HBs will be tested.
- An additional midstream urine sample must be provided at screening for a urine drug screening test. Drug screening involves analysis for amphetamines, benzodiazepines, cannabinoids, opioids and cocaine.
- In case of **rash**, safety blood samples (mandatory blood sample for safety in case of grade 3 or 4 rash and at the discretion of the investigator in case of grade 1 or 2 rash) might be taken at unscheduled visits as described in Section [9.8.6.1](#), and are to be processed by the local laboratory. The following parameters will need to be tested: AST, ALT, sedimentation rate, complete blood cell count (including hemoglobin, hematocrit, RBC count, WBC count, platelet count, neutrophils, lymphocytes, monocytes, eosinophils and basophils) and creatinine.
- In the event a subject develops clinical signs suggestive of muscle injury (eg, proximal weakness, myalgias), a thorough workup (eg, assessment of CK, CK muscle-brain [CK-MB] fraction, aldolase, myoglobin, calcium, phosphate, creatinine, and urinalysis) for muscle injury should be performed by a central laboratory as described in Section [9.8.6.6](#).

9.8.3. Electrocardiogram and Echocardiography

Electrocardiogram

Triplicate ECGs will be performed centrally at time points as indicated in the [Time and Events Schedule](#). Additional monitoring of ECG may be done, if in the opinion of the investigator, this is clinically indicated or if needed as part of the cardiac events management plan (see Section [9.8.6.7](#)). The mean of the triplicate ECGs need to be taken into account for decision making.

The subject will be instructed to rest in the supine position for 5 minutes before having an ECG assessment performed. If blood sampling or vital signs are scheduled at the same time point as the ECG recording, the procedures should preferably be performed in the following order: ECG, vital signs and blood draw.

The triplicate ECGs should be performed approximately 2 minutes apart over 10 minutes.

Twelve-lead ECGs will be recorded at a paper speed of 25 mm per second until 4 regular consecutive complexes are available. ECG machines will record timings of ECG measurements.

ECGs will be digitalized with local review by the investigator for immediate safety assessment. Digital ECG data will be transmitted to a centralized ECG over-read service provider. Over-read of the ECGs will be transmitted back to the site within 72 hours.

In case the measured QT/QTc value is >500 milliseconds or in case the QT/QTc value increases by >60 milliseconds from baseline, the sites need to check whether there is a technical problem with the ECG machine. It also needs to be checked if the ECG leads were correctly applied and if the tracing is free of artifacts that may interfere with QT measurements (see Section [9.8.6.7](#) for cardiac safety monitoring).

In case of a technical problem, the ECG recording has to be repeated after fixing the problem.

Any clinically relevant changes occurring from signing of ICF onwards until the subject's last study visit must be recorded on the Adverse Event Section of the eCRF.

Echocardiography

The cardiac monitoring requirements outlined in the protocol are critical and must be followed for all subjects. Transthoracic echocardiography will be performed at study approved facility to establish parameters including but not limited to LVEF at time points as indicated in the [Time and Events Schedule](#). The screening assessment will serve as baseline value. Additional echocardiography may be done, if in the opinion of the investigator, this is clinically indicated or if needed as part of the cardiac events management plan (see Section [9.8.6.7](#)).

Echocardiograms will be performed according to a standard protocol as described in the study manual. The same technique of echocardiography must be used for each assessment. A variety of echocardiographic parameters, including LVEF, will be quantitated and compared over time as

an assessment of safety by a central reader. These measures aim to reduce variability and enhance the precision of the study results.

Any clinically relevant changes occurring from signing of ICF onwards until the subject's last study visit must be recorded on the Adverse Event Section of the eCRF.

9.8.4. Vital Signs

Systolic and diastolic blood pressure and pulse/heart rate will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse/heart rate measurements should be taken supine and preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Any clinically relevant abnormalities occurring from signing of the ICF until the subject's last study visit must be recorded in the Adverse Event Section of the eCRF.

9.8.5. Physical Examination

To evaluate the subject's eligibility, a complete physical examination (including height, body weight and body systems and, if considered necessary by the investigator based on the subject's past and present medical history, breast, genitals or rectal examination) will be performed at screening. A targeted physical examination based on the medical history and overall clinical presentation (including body weight) will be performed at the time points indicated in the [Time and Events Schedule](#).

A complete physical examination includes the following: general appearance, eyes, ears, nose, throat, cardiovascular system, respiratory system, abdomen, and skin and mucous membranes. It does not include breast, genitals or rectal examination unless considered necessary by the investigator based on the subject's past and present medical history. A neurological and musculoskeletal examination as well as an examination of the lymph nodes will also be performed.

The height should be measured barefooted at the screening visit. To obtain the actual body weight, subjects must be weighed lightly clothed.

Any clinically relevant abnormalities occurring from signing of the ICF until the subject's last study visit must be recorded in the Adverse Event Section of the eCRF.

9.8.6. Management of Specific Toxicities

The safety monitoring and toxicity management plan described below takes into account the clinical safety data of AL-335, ODV, and SMV, target organs identified in nonclinical studies of AL-335, ODV, and SMV and known side effects of nucleotide analogs. Cardiac events and increased bilirubin are considered events of special interest for the AL-335+ODV+SMV combination program. Photosensitivity is considered an event of clinical interest.

9.8.6.1. Rash (Including Photosensitivity Conditions)

Subjects should be informed that they should contact their doctor immediately when they notice any skin reaction. The skin reaction should be evaluated in the clinic the same day (if possible) or the next day.

Photosensitivity conditions fall under the general umbrella of rash events. However, photosensitivity reactions can be differentiated from other rash events by careful history taking and general physical examination. Photosensitivity skin reactions are typically triggered by prolonged or extreme exposure to sunlight or artificial light. These reactions may present as an exaggerated sunburn reaction, usually affecting areas exposed to light (typically the face, ‘V’ area of the neck, extensor surfaces of the forearms, and the dorsa of the hands). Photosensitivity reactions can be prevented by avoiding excessive sun exposure and by the use of sun protection measures.

All rash events should be captured in the Adverse Event Section of the eCRF. A separate Rash page will be completed in case of a rash event. For rash events considered as potential photosensitivity reaction, a separate Photosensitivity page will be completed.

Monitoring of the evolution of rash (including photosensitivity reactions) will be performed based on the grade (severity) of the rash (see [Attachment 7](#)). At the discretion of the investigator, additional visits and assessments can be performed. Management of rash will take into account the protocol-defined procedures outlined in [Table 3](#).

Discontinuation of all study drugs (see [Section 6.2](#)) should be considered if a photosensitivity reaction occurs and subjects should be monitored until the reaction has resolved.

Table 3: Guidelines for Subjects Developing Rash Grade 1 to Grade 4

WHO Grade	Rash Definition	Investigator Action
Grade 1 Rash (with or without pruritus) ^{a,d}	erythema	May continue intake of study drugs at the investigator's discretion. Blood tests for safety (recommended) can be done at the investigator's discretion.
Grade 2 Rash (with or without pruritus) ^{b,d}	diffuse, maculopapular rash, OR dry desquamation	May continue intake of study drugs at the investigator's discretion. Blood tests for safety (recommended) can be done at the investigator's discretion.
Grade 3 Rash ^d	<ul style="list-style-type: none"> • vesiculation, moist desquamation, or ulceration OR • any cutaneous event with one of the following: <ul style="list-style-type: none"> - elevations in AST/ALT >2 x baseline value - fever >38°C or 100°F - eosinophils >1.00 x 10³/μL - serum sickness-like reaction 	Permanently discontinue the intake of SMV. AL-335 and ODV may be continued at the investigator's discretion. ^c Close monitoring is required to prevent progression of the rash. No rechallenge is allowed. Blood safety tests are mandatory. Referral to a dermatologist is required. At the discretion of the dermatologist a biopsy might be performed.
Grade 4 Rash ^d	<ul style="list-style-type: none"> • exfoliative dermatitis, OR • mucous membrane involvement, OR • erythema multiforme major, OR • Stevens-Johnson Syndrome, OR • necrosis requiring surgery. 	Permanently discontinue the intake of all study drugs. No rechallenge is allowed. Blood safety tests are mandatory. Referral to a dermatologist is required. A biopsy is required.

WHO: World Health Organization

^a In case the rash evolves from a grade 1 to a higher grade, management of the rash should follow the guidelines indicated for grade 2 or grade 3 or 4 rash, respectively (see [Attachment 7](#)).

^b In case the rash evolves from a grade 2 to a grade 3 or 4 rash, management of the rash should follow the guidelines specified for grade 3 or 4 rash (see [Attachment 7](#)).

^c Monotherapy with any of the study drugs is not allowed.

^d Determine if subject was adhering to the recommended sun-protective measures.

When safety blood samples are drawn as per the rash management guidelines, these should be processed by the local laboratory. The following parameters will need to be tested: AST, ALT, sedimentation rate, complete blood cell count (including hemoglobin, hematocrit, RBC count, WBC count, platelet count, neutrophils, lymphocytes, monocytes, eosinophils and basophils) and creatinine. The values of the local laboratory assessments need to be transcribed in the eCRF by the study-site personnel.

The subject may be treated symptomatically until the rash resolves. Oral antihistamines (eg, cetirizine, levocetirizine) and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. If systemic corticosteroids for longer than 24 hours are required for treatment of rash, the study drugs need to be permanently discontinued. If the rash is considered to be most likely due to concomitant illness or non-study drugs, standard management, including discontinuation of the likely causative agent, should be undertaken.

Dermatologist fees for evaluating subjects who experience a rash during the study will be reimbursed by the sponsor.

The following grades are based on the World Health Organization (WHO) Toxicity Grading Scale (see [Attachment 1](#)) with adaptations made by the sponsor.

Grade 1 Rash (With or Without Pruritus)

A grade 1 rash is defined as **erythema**.

- Subjects may continue the intake of study drugs (at the investigator's discretion).
- An unscheduled visit may be performed at the investigator's discretion as soon as possible after the subject contacts the investigator to report the AE.
- Assessment of safety blood samples by the local laboratory is recommended. The values of the local laboratory assessments need to be transcribed in the eCRF by the study-site personnel.

Unscheduled visits may also be performed after the initial rash assessment at the investigator's discretion for appropriate follow-up until resolution of the rash. At these visits, safety blood samples can be taken at the investigator's discretion. For these and all subsequent local laboratory blood sample assessments, the values of the assessments need to be transcribed in the eCRF by the study-site personnel.

The subject should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops. If appropriate, sun protection counseling should be provided.

In case the rash evolves from a grade 1 to a higher grade, management of the rash should follow the guidelines indicated for grade 2 or grade 3 to 4 rash, respectively.

Grade 2 Rash (With or Without Pruritus)

A grade 2 rash is defined as **diffuse, maculopapular rash OR dry desquamation**.

- Subjects may continue the intake of study drugs (at the investigator's discretion).
- An unscheduled visit for initial rash evaluation is required as soon as possible after the subject contacts the investigator to report the AE. If a visit is not possible, telephone contact with the subject should take place to collect information and to give advice on the necessary measures to be taken.

- Assessment of safety blood samples by the local laboratory is recommended. The values of the local laboratory assessments need to be transcribed in the eCRF by the study-site personnel.
- Referral to a dermatologist is optional but, when done, should occur preferably within 24 hours after the onset of the rash. A copy of the dermatologist's report should be made anonymous and will be collected by the monitor.

Unscheduled visits will also be performed after the initial rash assessment at the investigator's discretion for appropriate follow-up until resolution of the rash. At these visits, safety blood samples can be taken at the investigator's discretion. For these and all subsequent local laboratory blood sample assessments, the values of the assessments need to be transcribed in the eCRF by the study-site personnel.

The subject should be advised to contact the investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops. If appropriate, sun protection counseling should be provided.

In case the rash evolves from a grade 2 to a grade 3 to 4 rash, management of the rash should follow the guidelines specified for grade 3 to 4 rash.

Grade 3 or Grade 4 Rash

A grade 3 rash is defined as a rash associated with:

- vesiculation, moist desquamation, or ulceration OR
- any cutaneous event with one of the following:
 - elevations in AST/ALT >2 x baseline value,
 - fever >38°C or 100°F,
 - eosinophils >1.00 x10³/μL,
 - serum sickness-like reaction.

Subjects will permanently discontinue SMV. AL-335 and ODV may be continued at the investigator's discretion. Close monitoring is required to prevent progression of the rash.

A grade 4 rash is defined as:

- exfoliative dermatitis, OR
- mucous membrane involvement, OR
- erythema multiforme major, OR
- Stevens-Johnson Syndrome, OR
- necrosis requiring surgery.

Subjects will permanently discontinue all study drugs. No rechallenge is allowed.

An unscheduled (on-site) visit including a safety laboratory evaluation is required as soon as possible after the subject contacts the investigator to report the AE.

Assessment of safety blood samples by the local laboratory is required on the day of initial rash evaluation and the day thereafter (Days 0 and 1). The values of the local laboratory assessments need to be transcribed in the eCRF by the study-site personnel.

Referral to a dermatologist is required, preferably within 24 hours after the onset of the rash. A copy of the dermatologist report should be made anonymous and be collected by the monitor.

A biopsy may be performed at the discretion of the dermatologist for grade 3 rash and is required in case of a grade 4 rash as soon as possible after onset of rash. A copy of the dermatologist's report, and the biopsy if performed, should be made anonymous and be collected by the monitor.

Appropriate management should be undertaken and subjects should be followed until resolution of the rash or until clinical stability is reached.

A complete summary of the guidelines for rash management is given in [Attachment 7](#).

9.8.6.2. Acute Allergic Reaction

Oral antihistamines (eg, cetirizine, levocetirizine) and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. If treatment with systemic corticosteroids for longer than 24 hours would be required for an acute systemic allergic reaction, the study drugs need to be permanently discontinued.

Management of acute allergic reactions will take into account the protocol-defined procedures outlined in [Table 4](#).

WHO Toxicity Grade	Definitions	Investigator Action
Grade 1	Pruritus suggestive of an allergic reaction without rash	May continue study drugs or have their study drugs discontinued at the investigator's discretion.
Grade 2	Localized urticaria	May continue study drugs or have their study drugs discontinued at the investigator's discretion. Rechallenge is not allowed.
Grade 3	Generalized urticaria, or Angioedema	Permanently discontinue study drugs.
Grade 4	Anaphylaxis	Permanently discontinue study drugs.

Grade 1 (Pruritus Suggestive of an Allergic Reaction Without Rash)

Subjects may continue the intake of study drugs or have their study drugs discontinued at the investigator's discretion. Close clinical follow-up is recommended to monitor for any progression of the AE. Subjects should be advised to contact the investigator immediately if there is any worsening of symptoms.

Grade 2 (Localized Urticaria)

Subjects may continue the intake of study drugs or have their study drugs discontinued at the investigator's discretion. Close clinical follow-up is recommended to monitor for any progression of the AE. Subjects should be advised to contact the investigator immediately if there is any worsening of symptoms, in which case the subject will permanently discontinue the study drugs. Rechallenge is not allowed.

Grade 3 (Generalized Urticaria, Angioedema) and Grade 4 (Anaphylaxis)

Subjects will immediately and permanently discontinue the intake of study drugs. Rechallenge is not allowed. Subjects will be treated as clinically appropriate and should be followed until resolution of the AE.

9.8.6.3. Alanine Aminotransferase, Aspartate Aminotransferase and Bilirubin Elevations

Although an AST and ALT elevation of up to grade 3 is common in chronic HCV infection due to disease activity, treatment-emergent changes from baseline in ALT and AST levels should be carefully evaluated and results closely monitored, with unscheduled study visits if needed. Increases in bilirubin (both direct and indirect) have been observed during the first weeks of SMV therapy. These bilirubin elevations are caused by a competitive inhibition of biliary transporter systems in hepatocytes. Bilirubin elevations following initiation of SMV therapy are typically not associated with increases in ALT or AST levels and rapidly resolve after completion of SMV treatment. Bilirubin elevations have been observed to a much lesser extent with DAA regimens where SMV is administered without RBV compared to when it is administered with RBV.²²

Management of treatment-emergent AST, ALT, and/or bilirubin elevations will take into account the protocol-defined procedures outlined in [Table 5](#), [Table 6](#) and [Table 7](#).

Table 5: Treatment-emergent Grade 1 to Grade 4 Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) Elevation and Grade 1 to Grade 4 Total Bilirubin Elevation

WHO Toxicity Grade	AST or ALT, Ranges	Total Bilirubin, Ranges
Grade 1	≥ 1.25 to ≤ 2.5 x ULN	≥ 1.1 to ≤ 1.5 x ULN
Grade 2	> 2.5 to ≤ 5.0 x ULN	> 1.5 to ≤ 2.5 x ULN
Grade 3	> 5.0 to ≤ 10.0 x ULN	> 2.5 to ≤ 5.0 x ULN
Grade 4	> 10.0 x ULN	> 5.0 x ULN

Subjects may continue the intake of study drugs at the investigator's discretion in case of grade 1 and 2 increases in ALT and/or AST and/or grade 1, 2 and 3 increases in bilirubin levels. In case of a grade 3 ALT and/or AST increase or if a grade 4 ALT and/or AST ≤ 2 times the baseline value, this laboratory abnormality must be judged by the investigator to be either "not related" or "doubtfully related" to the study drugs in order to continue the intake of study drugs, in which case the intake of study drugs may be continued upon agreement with the sponsor. In subjects who continue the study drugs, close clinical follow-up is recommended to monitor for any progressive increases.

If a grade 4 ALT and/or AST value is >2 times the baseline value, a confirmatory measurement should be performed preferably within 72 hours after receipt of the results at the study site. If the grade 4 value is confirmed to be >2 times the baseline value, the study drugs should be discontinued (Table 6).

Any significant ALT flare, defined as either:

- ALT of $>2X$ ULN and $>2X$ the lowest previous ALT value measured during the study,
- OR
- any treatment-emergent grade 3 ALT elevation ($>5X$ ULN)

will trigger a thorough clinical work-up of the case by the investigator. This evaluation should include the assessment of serum HBV DNA (mandatory in subjects that are anti-HBc antibody positive at baseline).

In case of a grade 4 bilirubin value, subjects should have a confirmatory measurement within 72 hours after receipt of the results. If the grade 4 value is confirmed but not considered a sign of worsening liver disease, or if there is an identifiable cause for the value (eg, hereditary hyperbilirubinemia [Gilbert's syndrome] or concomitant medication associated event), subjects may continue the study drugs at the investigator's discretion (Table 7). Subjects who continue the study drugs should be carefully evaluated and close follow-up is recommended to monitor for progressive increase in bilirubin levels. If the grade 4 value is confirmed and is considered a sign of worsening liver disease, or if there is no identifiable explanation for the confirmed value, all study drugs should be discontinued.

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.

Subjects should be followed until return to predose baseline value or stabilization of ALT, AST and/or bilirubin elevation.

Table 6: Guidelines for Subjects Developing Alanine Aminotransferase (ALT) and/or Aspartate Aminotransferase (AST) Elevations

WHO Toxicity Grade	Ranges	Investigator Action
Grade 1	≥ 1.25 to ≤ 2.5 x ULN	May continue intake of study drugs at the investigator's discretion. Monitor for progressive increase in ALT and/or AST levels. In order to continue the study drugs, in case of a grade 3 ALT and/or AST increase, this laboratory abnormality should be considered "not related" or "doubtfully related" to the study drugs. Study drugs may be continued upon agreement with the sponsor.
Grade 2	>2.5 to ≤ 5.0 x ULN	
Grade 3	>5.0 to ≤ 10.0 x ULN	

Table 6: Guidelines for Subjects Developing Alanine Aminotransferase (ALT) and/or Aspartate Aminotransferase (AST) Elevations

WHO Toxicity Grade	Ranges	Investigator Action
Grade 4	>10.0 x ULN	<p>May continue study drugs at the investigator's discretion (upon agreement with the sponsor) if value is ≤ 2 times the baseline value and the event is considered "not related" or "doubtfully related" to study drugs. Subjects who continue should be carefully evaluated and close follow-up is recommended to monitor for progressive increase in ALT and/or AST levels.</p> <p>If the grade 4 ALT and/or AST value is >2 times the baseline value, a confirmatory measurement should be performed within 72 hours after receipt of the results. If the value is confirmed, all study drugs should be discontinued.</p>

Note: Any significant ALT flare, defined as either: (1) ALT of $>2X$ ULN and $>2X$ the lowest previous ALT value measured during the study, OR (2) any treatment-emergent grade 3 ALT elevation ($>5X$ ULN), will trigger a thorough clinical work-up of the case by the investigator. This evaluation should include the assessment of serum HBV DNA (mandatory in subjects that are anti-HBc antibody positive at baseline).

Table 7: Guidelines for Subjects Developing Bilirubin Elevations

WHO Toxicity Grade	Ranges	Investigator Action
Grade 1	≥ 1.1 to ≤ 1.5 x ULN	May continue intake of study drugs at the investigator's discretion. Monitor for progressive increase in bilirubin levels.
Grade 2	>1.5 to ≤ 2.5 x ULN	
Grade 3	>2.5 to ≤ 5.0 x ULN	
Grade 4	>5.0 x ULN	<p>A confirmatory measurement should be performed within <u>72 hours after receipt of the results</u>. If the value is confirmed and:</p> <ul style="list-style-type: none"> - Not considered a sign of worsening liver disease, or if there is an identifiable cause^a for the confirmed value, subjects may continue study drugs at the investigator's discretion. - Considered a sign of worsening liver disease, or if there is no identifiable explanation for the confirmed value, all study drugs should be discontinued. <p>Monitor for progressive increase in bilirubin levels.</p>

^a Eg, hereditary hyperbilirubinemia (Gilbert's syndrome) or concomitant medication associated event.

9.8.6.4. Clinical Hepatitis

Subjects should be monitored for any worsening of their hepatic disease and development of overt signs and symptoms (including increased fatigue, malaise, anorexia, nausea, dark urine, clay colored stools, bilirubinemia, jaundice, liver tenderness, hepatomegaly, severely increased serum transaminase levels).

Subjects with these signs and symptoms must seek medical attention immediately and have their hepatic parameters assessed. If severe worsening of hepatic disease is evident, all study drugs must be discontinued and the sponsor should be contacted.

9.8.6.5. Pancreatic Amylase or Lipase Elevations

For asymptomatic grade 1, grade 2 and grade 3 pancreatic amylase or lipase elevations with no history of treatment-emergent pancreatitis or concomitant lipase increase or signs of pancreatitis,

subjects should be carefully evaluated and closely followed. Study drugs may be continued at the discretion of the investigator. In the case of confirmed (within 72 hours) grade 4 pancreatic amylase or lipase elevations, or the presence of signs consistent with pancreatitis, all study drugs should be interrupted until the diagnosis of pancreatitis is excluded. If pancreatitis is confirmed, all study drugs should be permanently discontinued. An overview of the laboratory ranges to assign grading to a laboratory value for pancreatic amylase and lipase is provided in [Attachment 1](#).

Pancreatitis must be considered whenever a subject develops abdominal pain and nausea, vomiting, or elevated amylase or lipase, and study drugs should be interrupted until the diagnosis of pancreatitis is excluded.

9.8.6.6. Creatine Kinase

Because nucleosides, as a class, have a known risk of mitochondrial toxicity, which is often manifested as muscle injury, this study will systematically assess study subjects for laboratory abnormalities which might be present after muscle injury.

Specifically, CK is checked throughout the study treatment period.

Drug-induced myopathy is a diagnosis of exclusion as the differential diagnosis for muscle symptoms can be broad. If a subject develops clinical signs suggestive of muscle injury (eg, proximal weakness, myalgias), a thorough workup (eg, assessment of CK, CK-MB fraction, aldolase, myoglobin, calcium, phosphate, creatinine, and urinalysis) to understand the etiology for the myopathy should be undertaken by a central laboratory.

In all cases where a CK elevation triggers an evaluation of treatment stopping criteria (CK ≥ 3 x ULN), or where discontinuation of study drugs is planned due to the suspected muscle injury, the sponsor MUST be notified within 24 hours so that the clinical case and workup and treatment strategy can be discussed.

If a study subject's experiences treatment-emergent CK elevations (without a concomitant proportionate CK-MB elevation), the following treatment stopping criteria for CK elevations should be applied²⁹:

- In subjects (whether symptomatic or asymptomatic) without a clinical history or a differential diagnosis to suggest etiology of CK elevation (eg, recent exercise, other clinical comorbidities [eg, endocrinal, metabolic disorders] or exposure to medication with known risk of myopathy):
 - If CK is $\geq 20 \times$ ULN, immediately re-draw and repeat the test. If the repeat remains $\geq 20 \times$ ULN, discontinue AL-335. Continuation of ODV and SMV should be discussed with the sponsor on a case-by-case basis
 - If CK is $\geq 3 - < 20 \times$ ULN, continue study medication. Assess CK, CK-MB every ~72 hours (follow-up assessments) until the CK has normalized (follow-up assessments)

- If any follow-up CK assessment is $\geq 20 \times \text{ULN}$, discontinue AL-335. Continuation of ODV and SMV should be discussed with the sponsor on a case-by-case basis,
 - if the third follow-up CK assessment (ie, ~ 9 days after CK elevation was first recognized) is \geq the prior follow-up CK assessment, discontinue AL-335. Continuation of ODV and SMV should be discussed with the sponsor on a case-by-case basis,
 - If the CK is $>1.5 \times \text{ULN} - <3 \times \text{ULN}$, consider repeat CK, CK-MB in ~ 72 hours and continue testing until CK decreases. This might require an unscheduled visit.
- In subjects with a clinical history suggestive of a non-study drug related etiology for a CK elevation (eg, recent exercise, other clinical comorbidities [eg, endocrinal, metabolic disorders] or exposure to medication with known risk of myopathy), study medication may be continued. In such instances, the putative cause of the CK elevation should be addressed (eg, stop further exercise or the use of suspect medication) and the CK and CK-MB should be assessed every ~ 72 hours (=follow-up assessment):
 - If initial CK is $<5 \times \text{ULN}$, continue study medication unless follow-up CK assessments are increased to $\geq 20 \times \text{ULN}$,
 - If initial CK is $\geq 5 \times \text{ULN}$, continue study drug dosing and assessing follow-up CK and CK-MB every ~ 72 hours. If the third follow-up CK assessment (ie, ~ 9 days after CK elevation was first recognized) is \geq the prior follow-up CK assessment, discontinue AL-335. Continuation of ODV and SMV should be discussed with the sponsor on a case-by-case basis.

If CK-MB rises commensurately with elevation of CK, an assessment for cardiac ischemic injury (eg, EKG, troponin) should be initiated.

If a subject who experiences CK elevations also demonstrates clinical or laboratory evidence of renal insufficiency/damage or clinically significant muscle signs or symptoms (eg, proximal weakness), all study medication should be stopped regardless of the magnitude of the CK elevation.

9.8.6.7. Cardiac Safety Monitoring

Regular cardiac safety monitoring will be done in this study via assessments of AEs, serial ECGs and regular echocardiograms.

For all subjects enrolled in this study, LVEF at screening must be $\geq 55\%$ (see Section 4.2). Screening echocardiography will not only be used for assessing eligibility but will also be considered as the baseline measurement. Appearance or changes in symptoms or findings in echocardiogram may trigger the following treatment stopping criteria²⁵:

A. Asymptomatic patients with no clinical evidence of congestive heart failure:

1. If the absolute decrease from baseline in LVEF is $\geq 10\%$ (eg, 59% to 49%) and resulting in an LVEF of $<50\%$, discontinue AL-335, ODV, and SMV.

2. If the absolute decrease from baseline in LVEF is $>5\%$ and $\leq 10\%$, or $>10\%$ and resulting in an LVEF $\geq 50\%$, an assessment of the subject's clinical status, including symptoms, physical exam, and other clinical parameters should be made before deciding whether to stop or continue study drugs.
- B. For subjects with symptoms (eg, dyspnea, orthopnea) or signs of congestive heart failure (eg, S3 gallop, pedal edema, pulmonary edema):
1. If the absolute decrease from baseline in LVEF is $\geq 5\%$, discontinue AL-335, ODV, and SMV.

For all cases described above, a mandatory assessment and urgent cardiology referral should be initiated. The LVEF decrease must be reported to the Medical Monitor within 24 hours so that the clinical case and workup and treatment strategy can be discussed.

The cardiology assessment should include, but is not limited to, the following:

- Review of the cardiopulmonary body systems,
- Chest X ray,
- Troponin I assessment,
- 12 lead ECG, and
- Repeat echocardiography (at study approved facility).

Echocardiography must be performed at study approved facility on any subject who develops symptoms or signs of possible congestive heart failure (eg, dyspnea, orthopnea, S3 gallop, pedal edema) during the study, regardless of the timing of such symptoms, including during the follow-up period.

For all subjects enrolled in this study, triplicate ECGs will be taken at screening and at regular intervals during the study period. Appearance or changes in symptoms or clinically significant findings in ECG may trigger the following treatment stopping criteria:

1. If a first degree AV block is diagnosed and
 - a. The PR interval is >200 milliseconds but ≤ 240 milliseconds, study drugs can be continued. Close monitoring with weekly ECG is recommended.
 - b. The PR interval is >240 milliseconds but ≤ 300 milliseconds (confirmed by a repeat triplicate analysis at least 30 minutes after the initial assessment), an assessment of the subject's clinical status, including symptoms, physical examination and other clinical parameters should be made and the study drugs can be continued. Close monitoring with weekly ECG is recommended.
 - c. The PR interval is >300 milliseconds (confirmed by a repeat triplicate analysis at least 30 minutes after the initial assessment, irrespective of presence or absence of clinical symptoms), ODV must be discontinued. AL-335 and SMV may be continued at the investigator's discretion.

2. If a second degree or higher AV block is diagnosed (confirmed by a repeat triplicate analysis at least 30 minutes after the initial assessment and irrespective of presence or absence of clinical symptoms), ODV must be discontinued. AL-335 and SMV may be continued at the investigator's discretion.
3. In case the QTcF value is >500 milliseconds (confirmed by a repeat triplicate analysis at least 30 minutes after the initial assessment and irrespective of presence or absence of clinical symptoms), ODV must be discontinued. AL-335 and SMV may be continued at the investigator's discretion.
In case the QTc value increases by >60 milliseconds from baseline, thorough evaluation of the clinical case and discussion with the sponsor is required to assess further treatment strategy.

All events described above, should trigger a thorough cardiac assessment (ECG, echocardiography, and cardiology referral) and follow up (eg, weekly ECG until PR interval is <240 milliseconds). These events as well as any cardiac event that is serious, severe, or life-threatening must be reported to the Medical Monitor within 24 hours so that the clinical case workup and treatment strategy can be discussed.

9.8.6.8. Renal Safety Monitoring

Renal safety will be monitored by evaluating urine dipstick, in particular urinary proteins, serum creatinine levels, eGFR, and serum chemistry results. The investigator should closely monitor for disturbances in serum creatinine and eGFR. In case renal complications develop, subjects must be treated as clinically appropriate.

The study drugs may be continued if the renal complication is considered not to be related to the study drugs in the opinion of the investigator.

If the eGFR value is <30 mL/min, the value must be confirmed by repeat testing during an unscheduled visit preferably within 1 week after the results become available to the study site. If the eGFR value is confirmed to be <30 mL/min, all study drugs must be interrupted and renal function will be followed as clinically appropriate. The possibility of restarting treatment should be discussed with the sponsor on a case-by-case basis.

9.8.6.9. Other Toxicities

Note: For grade 3 or grade 4 treatment-emergent laboratory abnormalities, subjects should have a confirmatory measurement performed by the local laboratory. The management scheme below is for confirmed treatment-emergent laboratory abnormalities and AEs not included in the sections above and not for isolated and/or non-confirmed events.

Grade 1

Subjects who develop a grade 1 AE or grade 1 laboratory abnormality may continue the intake of study drugs.

Grade 2

Subjects who develop a grade 2 AE or grade 2 laboratory abnormality may continue or may discontinue the intake of study drugs based on the investigator's clinical judgment.

Grade 3

Subjects who develop a grade 3 AE or grade 3 laboratory abnormality may continue or may discontinue the intake of study drugs at the investigator's discretion if the grade 3 AE or laboratory abnormality is judged by the investigator to be either "not related" or "doubtful relation" to any of the study drugs.

For subjects who develop a grade 3 AE or grade 3 laboratory abnormality at least possibly related to any of the study drugs, the sponsor needs to be informed and treatment can only be continued if agreed upon by the sponsor and investigator.

Grade 4

Subjects who develop a grade 4 AE or grade 4 laboratory abnormality may continue or may discontinue the intake of study drugs at the investigator's discretion if the grade 4 AE or laboratory abnormality is judged by the investigator to be either "not related" or of "doubtful relation" to any of the study drugs.

Subjects who develop a grade 4 AE or grade 4 laboratory abnormality at least possibly related to any of the study drugs should discontinue all study drugs.

9.9. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the [Time and Events Schedule](#) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided to the study sites. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

10. SUBJECT COMPLETION/WITHDRAWAL**10.1. Completion**

A subject will be considered to have completed the study if he or she has completed the assessments at the W24 FU visit.

10.2. Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before the end of the treatment regimen, this will not result in automatic withdrawal of the subject from the study.

Study drug(s) should be discontinued if (see Section 9.8.6 for more details):

- The investigator believes that for safety reasons (eg, AE) it is in the best interest of the subject to discontinue study treatment.
- The subject becomes pregnant.
- The subject has a grade 4 rash; see Section 9.8.6.1.
- The subject has a grade 3 or 4 allergic reaction; see Section 9.8.6.2.
- The subject has a confirmed grade 4 ALT and/or AST value that is >2 times the baseline value; see Section 9.8.6.3.
- 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; see Section 9.8.6.3.
- The subject has severe worsening of hepatic disease; see Section 9.8.6.4.
- The subject has a confirmed diagnosis of pancreatitis; see Section 9.8.6.5.
- The subject has clinical signs suggestive of muscle injury; see Section 9.8.6.6.
- The subject has evidence of cardiac toxicity, see Section 9.8.6.7.
- The subject has a grade 4 AE at least possibly related to 1 of the study drugs; see Section 9.8.6.9.

Note: For laboratory abnormalities triggering treatment discontinuation, see the toxicity management plan described in Section 9.8.6.

- The subject requires treatment with any of the medications reported on the list of disallowed medications; see Section 8.
- The subject meets a treatment stopping rule for viral breakthrough (see Section 6.3).
- One of the study treatment stopping rules is met (see Section 6.4).

If a subject prematurely discontinues study treatment for above-mentioned reasons, he or she will proceed with a treatment withdrawal visit and will subsequently enter the follow-up phase. Additional unscheduled visits may be performed for safety/tolerability reasons, if needed.

10.3. Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up,
- Withdrawal of consent,
- Death.

If a subject is lost to follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

Subjects who withdraw consent during the treatment or follow-up phase will be offered an optional safety follow-up visit, at which the assessments from the W4 FU visit need to be performed. Any subject who withdraws consent during the follow-up phase and/or notifies the site he or she will not return for study visits, will be invited to do a follow-up visit at the time of withdrawal to complete the full set of protocol procedures as scheduled for the W24 FU visit. However, all possible efforts should be made to ensure that subjects complete the study.

Subjects who withdraw consent from the PK substudies or who withdraw their optional consent for the optional host DNA research (see Section 16.2.3) can still continue to participate in the main study.

If the subject enrolls in a clinical study with an investigational drug (including investigational vaccines), the subject will have to withdraw from the present study first.

Withdrawal of Consent for Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Section 16.2.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

Safety, efficacy, and/or pharmacokinetic data from this study may be pooled with data from the Phase 2a AL-335-604 study and potentially other similarly performed studies to assess the combination regimen of AL-335, ODV and SMV. This will increase the sample size for the different subgroups/duration groups and provide for more accurate estimates for safety and efficacy endpoints. The details of this combined analysis will be outlined in a separate analysis plan.

11.1. Subject Information

For all subjects who receive at least one dose of study drug descriptive statistics will be provided.

11.2. Sample Size Determination

The description of the sizing for the study based on 300 subjects is provided below.

The sample size consideration is based on non-inferiority testing against performance benchmark 98% based on historical data (ASTRAL 1-3 studies)^{4,9,10} 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.³⁶ 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%).

In addition, with a total sample size of 150 subjects in each treatment arm (300 subjects in total), the probability to observe an AE with an incidence of 0.1%, 0.5%, 0.8%, and 1% are 13.9% (25.9%), 52.9% (77.8%), 70.0% (91.0%), and 77.9% (95.1%), respectively.

To aid in the evaluation of efficacy of the 3-DAA regimens, Bayesian posterior probabilities on the true SVR will be calculated using uninformative prior (Jeffreys prior) and provided to the DRC (see Section 11.11). The posterior probability that the true SVR exceeds certain thresholds (eg, 90%, 95%) will be generated. Posterior probabilities associated with alternative thresholds may also be provided and are intended to aid the DRC in the interim evaluations of efficacy. Similar computations may also be provided for safety endpoints of interest.

In conclusion, a total sample size of 300 subjects in the study is considered sufficient to explore the efficacy, safety, tolerability and PK of the 3-DAA regimen in this study.

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 a probability to observe an 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.

11.3. Efficacy Analyses

The primary efficacy analyses will be performed on the intent-to-treat (ITT) population, defined as all subjects who received at least one dose of study drug (AL-335, ODV, or SMV). Additional sensitivity analyses on efficacy may be performed after excluding subjects with early treatment discontinuation due to non-virologic reasons or missing data at SVR12 time point, as well as on the per-protocol population, defined as the ITT population excluding subjects with a pre-specified major protocol deviation.

An interim analysis is planned at the SVR4 time point, ie, when all subjects have reached the SVR4 (W4 FU visit) time point or discontinued earlier.

The primary analyses will be performed when all subjects have reached the SVR12 time point or discontinued earlier. Additional interim analyses may be conducted if needed to support clinical development.

The final analysis will be performed when all subjects have completed the last study-related visit (SVR24 time point; W24 FU visit) or discontinued earlier.

For the primary endpoint, for each treatment arm, the proportion of subjects who achieve SVR12 will be calculated. A 2-sided 95% CI will be constructed around the SVR12. The lower limit of the 95% CI of the SVR12 rate will be compared against the performance benchmark for non-inferiority. A lower bound of the 2-sided 95% CI $\geq 88\%$ will satisfy the hypothesis for non-inferiority in at least one treatment arm. Since this is a Phase 2 study, the primary goal in efficacy analyses is to obtain a reliable estimation of SVR12 and then compare it to the historical control for non-inferiority in order to select the optimum regimen for further evaluation in Phase 3.. A fixed sequence procedure will be used to adjust for multiple (two) confidence intervals (each arm is compared to the historical control). Since the clinical development strategy is to establish the shortest efficacious treatment duration, the 6-week regimen arm is tested first and only if this is found to be non-inferior, the test will be performed for the 8-week regimen. The confidence level is two-sided 95% for both confidence intervals.

Additional sensitivity analysis may be performed by applying different imputation rules for missing data. Missing data patterns will be analyzed and described in detail.

To aid in the evaluation of efficacy of the 3-DAA regimens, Bayesian posterior probabilities on the true SVR will be calculated using uninformative prior.

Descriptive statistics will be used for all efficacy endpoints and will be tabulated by treatment arm.

The potential association between treatment outcome and baseline factors such as stratification factors, geno/subtype, and baseline HCV RNA levels will be explored by subgroup analysis.

11.3.1. Criteria for Endpoints

Efficacy Parameters

HCV RNA levels will be used to determine the response to HCV treatment: virologic response and failure (on-treatment failure and viral relapse). Refer to the [Definitions of Terms](#) for more details.

Patient-reported Outcomes

The clinical importance of mean changes from baseline in PRO scores will be interpreted using the following guidelines:

- EQ-5D-5L VAS mean change $\geq \pm 8.2$ points
- FSS mean change $\geq \pm 0.7$ points

Values demonstrated to reflect clinically important changes in mean scores for CLDQ-HCV summary and domain scores, and SF-36v2 component and domain scores in subjects with chronic HCV infection will be provided in the SAP if available to aid in interpreting the clinical significance of mean PRO scores changes over time.

Proposed threshold values indicating clinically important improvement or worsening in a subject's score for each PRO score are listed in [Table 8](#).

Table 8: Proposed Threshold Values Indicating Clinically Important Improvement or Worsening in Individual Subject's PRO Scores

PRO Endpoints	Clinically Important Worsening in Outcome	Clinically Important Improvement in Outcome
CLDQ-HCV		
domain scores (1-7 scale)	≥ 0.5 point decrease	≥ 0.5 point increase
summary score	≥ 10 point decrease	≥ 10 point increase
EQ-5D VAS score	≥ 10 point decrease	≥ 10 point increase
FSS Total score	≥ 1 point increase	≥ 1 point decrease
SF-36v2		
PCS	≥ 5 point decrease	≥ 5 point increase
MCS	≥ 5 point decrease	≥ 5 point increase
8 domain scores	≥ 10 point decrease	≥ 10 point increase

11.3.2. Resistance Determination Analyses

The results of viral sequencing will be evaluated by the sponsor virologist. Pre-treatment polymorphisms in the HCV NS3/4A, NS5A and NS5B regions in all subjects and relevant changes in the HCV NS3/4A, NS5A and NS5B regions in subjects not achieving SVR will be tabulated and described. The effect of pre-treatment NS3/4A, NS5A and NS5B polymorphisms on treatment outcome will be explored. These changes in viral sequence will not be regarded as AEs or SAEs.

Additional exploratory characterization of the viral genotype and phenotype may be performed and will be reported accordingly.

11.3.3. Patient-reported Outcomes Analyses

Patient-reported outcomes scores will be analyzed descriptively by treatment arm as mean scores over time, and evaluated based on the proportion of subjects experiencing a clinically important improvement or worsening in PRO scores from baseline during study drug treatment and at follow-up visits at Weeks 4, 12, and 24. Time and duration of clinically important improvement or worsening in PRO scores will be analyzed and reported.

11.4. Pharmacokinetic Analyses

PopPK Analysis for all Subjects

The PK samples taken from all subjects in the study (see [Time and Events Schedule](#)), as well as the sparse and rich PK samples collected in the PK substudies (see [Time and Events Schedule: PK Assessments in PK Substudies](#)) will be used for popPK model development and/or popPK model update. PopPK analysis of plasma concentration-time data of AL-335 and its metabolites, ODV, and SMV from all subjects (including those of PK substudies) will be performed using nonlinear mixed-effects modeling. Population PK modeling will be used to describe the concentration-time profiles and estimate the exposure parameters (AUC_{24h} and C_{0h}) of AL-335 (and metabolites), ODV, and SMV. Available baseline subject characteristics (demographics, body weight, laboratory variables, genotype, etc.) may be explored as potential covariates affecting PK parameters. Details will be given in a popPK analysis plan and the results of the popPK analysis will be presented in a separate popPK report.

Data will be listed for all subjects with available plasma concentrations. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of PK (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All subjects and samples excluded from the analysis will be clearly documented in the popPK report.

Descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, maximum and geometric mean will be performed for all individually estimated exposure parameters (AUC_{24h} and C_{0h}) of AL-335 and its metabolites, ODV, and SMV.

Non-compartmental PK Analysis for Rich PK Sampling in the PK Substudy

For the intensive PK samples of the rich PK substudy, non-compartmental PK analysis of AL-335 and its metabolites, ODV, and SMV will be performed using actual sampling time and plasma concentrations obtained from rich serial PK blood sampling at Week 4 for approximately 20 subjects (arms A and B combined) (see [Section 9.3](#)). Descriptive statistics will be provided for the PK parameters derived, including graphical analyses of the data.

Analyses of protein binding and/or metabolite profiling may be conducted at the sponsor's discretion and reported separately from this study.

11.5. Pharmacokinetic/Pharmacodynamic Analyses

Relationships of AL-335 (and its metabolites), ODV, and SMV population-derived exposure parameters (AUC_{24h} and C_{0h}) with SVR12 and with safety endpoints will be explored. These relationships will be presented in a graphical display.

11.6. Pharmacogenomic Analyses

Baseline *IL28B* genotyping data will be tabulated. Subgroup analyses will be done to explore the effect of the *IL28B* genotype (rs12979860) on efficacy by means of descriptive statistics and frequency tabulations.

Where locally permitted and upon consent of the subject (in addition to the consent for the main part of the study) an additional optional blood sample will be collected at baseline for exploratory host DNA research related to AL-335 (and metabolites), ODV, and SMV, and limited to genes involved in the metabolism of the study drugs as well as drug transporter genes. The statistical approach for analyzing the exploratory host DNA research may depend on the objective of the analyses (treatment response, side effects, metabolism) and possibly relevant genes at the time of analysis.

11.7. Occupational/Employment Status Analysis

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

11.8. Medical Resource Utilization

MRU data will be descriptively summarized by treatment arm over time.

11.9. Safety Analyses

Safety will be evaluated by means of AEs, clinical laboratory tests, vital signs, ECGs, echocardiography and physical examinations. The safety analysis will be done for each study phase separately (screening, treatment, and follow-up).

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). Treatment-emergent AEs are AEs with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least one occurrence of the given event will be summarized by treatment arm. In addition, comparisons between treatment arms will be provided if appropriate.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or a SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary table of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. A graphical presentation of changes in laboratory tests will be made as applicable.

Laboratory abnormalities will be assessed according to the WHO Toxicity Grading Scale (see [Attachment 1](#)) and the normal ranges of the clinical laboratory. Laboratory abnormalities will be tabulated by treatment arm.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values (the initial ECG will be used as baseline).

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, RR interval, QT interval, QTcF (primary correction method)¹¹ and QT interval corrected for heart rate according to Bazett² QT correction.

QTc data will be analyzed according to the International Conference on Harmonisation (ICH) E14 Step 4 Guidance (May 2005)¹⁴ (see also [Attachment 2](#)).

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with QTc interval >450 milliseconds, >480 milliseconds, or >500 milliseconds will be summarized, as will the percentage of subjects with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

All important abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

Echocardiography

Echocardiographic data will be summarized by key parameters, including LVEF. Descriptive statistics for the echocardiography parameters will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Descriptive statistics of LVEF and mean change from baseline will be summarized at each scheduled time point. Time of onset for LVEF decrease and duration, the percentage of subjects with a decrease in LVEF >10% from baseline, with reversible decrease in LVEF and with no resolution of the decreased LVEF will be summarized.

All clinically significant abnormal findings on echocardiography that are changes from baseline readings will be reported.

Vital Signs

Descriptive statistics of pulse/heart rate, and blood pressure (systolic and diastolic) (supine) values and changes from baseline will be summarized at each scheduled time point. The

percentage of subjects with values beyond clinically important limits will be summarized (see [Attachment 2](#)).

Physical Examination

Physical examination findings will be listed

11.10. Interim Analysis

An interim analysis is planned at the SVR4 time point, ie, when all subjects have reached the SVR4 (W4 FU visit) time point or discontinued earlier. Additional interim analyses may be conducted if needed to support clinical development.

Since this is an open-label study, there is no need to unblind the treatment. An interim analysis SAP will be prepared before the interim analyses.

11.11. Data Review Committee

A DRC will be established to monitor data on a regular basis to ensure the continuing safety, efficacy and well-being of the subjects enrolled in this study. The DRC will review the HCV RNA data and evaluate the incidence of treatment failure due to virologic reasons (relapse as well as on treatment virological failure) on a regular basis to monitor the efficacy of the regimen in this target population and to ensure that the risks to the subject is balanced by the anticipated benefits. Upon review of the HCV RNA data, the DRC will make study conduct recommendations, which may include, but is not limited to, continuing the study without modifications and/or implementation of treatment extension.

Emerging safety data from this study will be reviewed at predetermined intervals. As a part of these safety evaluations, the DRC will also review AEs considered as anticipated for this patient population (see [Attachment 8](#)).

After the review of the accumulating efficacy and safety data from this study and consideration of data from other completed and ongoing studies, including the Phase 2a study AL-335-604, the DRC will make recommendations regarding the continuation of the study.

In addition the DRC is responsible for the ad-hoc safety assessment of cardiac events that potentially qualify for a study treatment stopping rule (see Section [6.4](#)).

In case of substantial changes to the study conduct, other than the treatment extension described in this protocol (see Section [3.1](#)), an amendment to the protocol will be issued and submitted for approval by the competent authorities.

The DRC will consist of at least one medical expert in the relevant therapeutic area, one cardiologist (for the review and interpretation of any cardiac safety data) and at least one statistician. The DRC responsibilities, authorities, and operating procedures (including predefined futility criteria treatment arms) will be documented in the DRC charter. The DRC is a committee within the sponsor's organization that is independent of the sponsor's study team.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

The sponsor shall notify the concerned Health Authorities of any urgent safety measures and potential serious breaches in accordance with the sponsor's internal procedures and in line with the timelines defined in local regulations.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per ICH.)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening
(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect,
- Is a suspected transmission of any infectious agent via a medicinal product,

- Is Medically Important*.

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For AL-335, ODV, and SMV the expectedness of an AE will be determined by whether or not it is listed in the IB.

Adverse Event Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the drug.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the general categorical descriptors outlined in the WHO Toxicity Grading Scale in [Attachment 1](#).

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug,
- Suspected abuse/misuse of a sponsor study drug,
- Inadvertent or accidental exposure to a sponsor study drug,
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion).

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed ICF is obtained until the subject's last study visit. Serious AEs must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in [Attachment 8](#).

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number,
- Statement, in the local language(s), that the subject is participating in a clinical study,
- Investigator's name and 24-hour contact telephone number,
- Local sponsor's name and 24-hour contact telephone number (for medical staff only),
- Site number,
- Subject number.

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves,
- The event stabilizes,
- The event returns to baseline, if a baseline value/status is available,
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct,
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Suspected transmission of an infectious agent by a medicinal product will be reported as a SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the

course of a subject's participation in a study must be reported as a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility),
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE,
- Hospitalization in view of the logistic challenges related to the visit schedule of the rich PK substudy (see Section 9.3 and [Time and Events Schedule: PK Assessments in PK Substudies](#)).

The cause of death of a subject in a, whether or not the event is expected or associated with the study drug, is considered a SAE.

12.3.3. Pregnancy

Pregnancies in female subjects and female partners of male subjects will be reported from the time a signed and dated ICF is obtained until the end of the study.

Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed on the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has

established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The AL-335 supplied for this study will be formulated as 400 mg tablets. It will be manufactured by Patheon Can and provided under the responsibility of the sponsor. Refer to the current IB for a list of excipients.¹⁶

The ODV supplied for this study is formulated as 25 mg film-coated tablets. It will be manufactured by Catalent US and provided under the responsibility of the sponsor. Refer to the current IB for a list of excipients.¹⁵

The SMV supplied for this study will be formulated as 75 mg capsules (G034). It will be manufactured and provided under the responsibility of the sponsor. Refer to the current IB for a list of excipients.^{17,18}

14.2. Packaging

The study drug will be packaged in individual subject kits. Each kit will consist of the following study drugs, which will be packaged in bottles.

Study drug	Package	Pharmaceutical form
AL-335: 400 mg	30 count bottle	Tablet
ODV: 25 mg	30 count bottle	Tablet
SMV: 75 mg	30 count bottle	Capsule

All study drug will be dispensed in child-resistant packaging.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study drug must be stored at room temperature.

Refer to the pharmacy manual/study site investigational product manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Whenever a subject brings his or her study drug to the study site for pill count, this is not seen as a return of supplies. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- IBs for AL-335, ODV, and SMV, and their addenda,
- Pharmacy manual/study site investigational product manual,
- Echocardiography manual,
- ECG manual,
- IWRS manual,
- Laboratory manual,
- Medication diaries,
- On-demand access to study-specific training directly on the electronic PRO (ePRO) device,
- Touch-screen computer for entry of ePRO data,

- ePRO Site User Manual,
- Electronic Data Capture (eDC) Manual,
- Sample ICF,
- Contact information page.

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments,
- Sponsor-approved ICFs (and any other written materials to be provided to the subjects),
- Investigator's Brochure (or equivalent information) and amendments/addenda,
- Sponsor-approved subject recruiting materials,
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable,
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB),

-
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects,
 - Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct),
- Revision(s) to ICF and any other written materials to be provided to subjects,
- If applicable, new or revised subject recruiting materials approved by the sponsor,
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable,
- New edition(s) of the IB and amendments/addenda,
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually),
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug,
- New information that may adversely affect the safety of the subjects or the conduct of the study,
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects,
- Report of deaths of subjects under the investigator's care,
- Notification if a new investigator is responsible for the study at the site,
- Development Safety Update Report and Line Listings, where applicable,
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF will be given to the subject.

At selected study sites participating in the PK substudies, the ICF will contain a separate section explaining the PK substudy and separate consent can be given for this substudy.

Where local regulations require, a separate ICF may be used for the required DNA (*IL28B* genotype) component of the study.

Subjects will be asked for consent to provide an optional sample for host DNA research (where locally permitted). After informed consent for the study is appropriately obtained, the subject will be asked to consent, in addition to consenting for the main obligatory part of the study, indicating agreement to participate in the optional research component. Refusal to participate in

the optional research will not affect ineligibility for the study. A copy of this signed ICF will be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

If any new information that may be relevant to the subject's willingness to participate in the study becomes available, the investigator should inform the subject and ensure the subject signs a revised consent form, if applicable.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, pharmacodynamic, and PK research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand AL-335, ODV, and SMV, to understand HCV infection, to understand differential drug responders, and to develop

tests/assays related to AL-335, ODV, and SMV and HCV infection. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator,
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee,
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study,
- Regulatory authority approval or notification, if applicable,
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable,
- Documentation of investigator qualifications (eg, curriculum vitae),
- Completed investigator financial disclosure form from the principal investigator, where required,
- Signed and dated clinical trial agreement, which includes the financial agreement,
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators,
- Documentation of subinvestigator qualifications (eg, curriculum vitae),
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable,
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification

and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the eCRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race,
- History of smoking,
- Blood pressure and pulse/heart rate,
- Height and weight,
- Details of physical examination,
- MRU data.

The PRO assessments will be completed by subjects on touch-screen computers provided at the study site. The results will be recorded directly into the ePRO database and will be considered source data.

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician, or
- Complete history of medical notes at the site,
- Discharge summaries.

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF, and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. Data must be entered into eCRFs in English. Study site personnel must complete the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool.

If corrections to a eCRF are needed after the initial entry into the eCRF, this can be done in 3 different ways:

- Study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, direct transmission of clinical laboratory data from a central laboratory, and direct transmission of PRO data to the ePRO vendor database and then into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study

documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of subjects by the investigator;
- Discontinuation of further study drug development.

17.10. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding SMV or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or PK research data, generated

as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of SMV, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain eCRF data from all study sites that participated in the study, laboratory data from the selected laboratory and PRO data from the ePRO vendor database, that were transmitted into the sponsor's database. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic or PK analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant

contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

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^a Odalasvir Investigator’s Brochure Edition 6, Addendum 4 replaces all prior addenda; ie, Addendum 1, 2 and 3 are obsolete.

ATTACHMENTS

Attachment 1: WHO Scale for Determining the Severity of Adverse Events

February 2003

ABBREVIATIONS (used in the table):

ULN = Upper Limit of Normal

LLN = Lower Limit of Normal

R_x = Therapy

IV = Intravenous

FEV₁ = forced expiratory volume in 1 second

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1	Mild	Transient or mild discomfort (<48 hours); no medical intervention/therapy required.
GRADE 2	Moderate	Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/ therapy required.
GRADE 3	Severe	Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalizations possible.
GRADE 4	Potentially life-threatening^a	Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care probable.

^a Revised by the sponsor

COMMENTS REGARDING THE USE OF THESE TABLES

- For parameters not included in the following Toxicity Tables, sites should refer to the “Guide For Estimating Severity Grade” located above.
- Criteria are generally grouped by body system. Some protocols may have additional protocol-specific grading criteria, which will supersede the use of these tables for specified criteria.

Item	Grade 1	Grade 2	Grade 3	Grade 4
Hematology				
Hemoglobin	9.5-10.5 gm/dL	8.0-9.4 gm/dL	6.5-7.9 gm/dL	<6.5 gm/dL
Absolute Neutrophil Count	1000-1500/mm ³	750-999/mm ³	500-749/mm ³	<500/mm ³
Platelets	75,000-99,000/mm ³	50,000-74,999/mm ³	20,000-49,999/mm ³	<20,000/mm ³
Prothrombin Time (PT)	≥1.01 to ≤1.25 x ULN	>1.25 to ≤1.50 x ULN	>1.50 to ≤3.00 x ULN	>3.00 x ULN
Activated Partial Thromboplastin Time (aPTT)	≥1.01 to ≤1.66 x ULN	>1.66 to ≤2.33 x ULN	>2.33 to ≤3.00 x ULN	>3.00 x ULN
Fibrinogen	≥0.75 to ≤0.99 x LLN	≥0.50 to <0.75 x LLN	≥0.25 to <0.50 x LLN	<0.25 x LLN
Fibrin Split Product	20-40 mcg/mL	41-50 mcg/mL	51-60 mcg/mL	>60 mcg/mL
Methemoglobin	5.0-9.9%	10.0-14.9%	15.0-19.9%	>20.0%
Liver Enzymes				
AST (SGOT)	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
ALT (SGPT)	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
Gamma-glutamyltransferase	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
Alkaline Phosphatase	≥1.25 to ≤2.50 x ULN	>2.50 to ≤5.00 x ULN	>5.00 to ≤10.00 x ULN	>10.00 x ULN
Amylase	≥1.1 to ≤1.5 x ULN	>1.5 to ≤2.0 x ULN	>2.0 to ≤5.0 x ULN	>5.0 x ULN
Chemistries				
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	<116 mEq/L or mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	>165 mEq/L or mental status changes or seizures
Hypokalemia	3.0-3.4 mEq/L	2.5-2.9 mEq/L	2.0-2.4 mEq/L or intensive replacement Rx required or hospitalization required	<2.0 mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6-6.0 mEq/L	6.1-6.5 mEq/L	6.6-7.0 mEq/L	>7.0 mEq/L or life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39 mg/dL	<30 mg/dL or mental status changes or coma
Hyperglycemia (non-fasting and no prior diabetes)	116-160 mg/dL	161-250 mg/dL	251-500 mg/dL	>500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4-7.8 mg/dL	7.7-7.0 mg/dL	6.9-6.1 mg/dL	<6.1 mg/dL or life-threatening arrhythmia or tetany

Item	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia (corrected for albumin)	10.6-11.5 mg/dL	11.6-12.5 mg/dL	12.6-13.5 mg/dL	>13.5 mg/dL or life-threatening arrhythmia
Hypomagnesemia	1.4-1.2 mEq/L	1.1-0.9 mEq/L	0.8-0.6 mEq/L	<0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0-2.4 mg/dL	1.5-1.9 mg/dL or replacement Rx required	1.0-1.4 mg/dL intensive Rx or hospitalization required	<1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	≥ 1.1 to ≤ 1.5 x ULN	> 1.5 to ≤ 2.5 x ULN	> 2.5 to ≤ 5.0 x ULN	> 5.0 x ULN
Lipase ^a	≥ 1.1 to ≤ 1.5 x ULN	> 1.5 to ≤ 3.0 x ULN	> 3.0 to ≤ 5.0 x ULN	> 5.0 x ULN
Blood urea nitrogen	≥ 1.25 to ≤ 2.50 x ULN	> 2.50 to ≤ 5.00 x ULN	> 5.00 to ≤ 10.00 x ULN	> 10.00 x ULN
Creatinine	≥ 1.1 to ≤ 1.5 x ULN	> 1.5 to ≤ 3.0 x ULN	> 3.0 to ≤ 6.0 x ULN	> 6.0 x ULN or required dialysis
Urinalysis				
Proteinuria	1+ or <0.3% or <3g/L or 200 mg – 1 gm loss/day	2-3+ or 0.3-1.0% or 3-10 g/L or 1-2 gm loss/day	4+ or >1.0% or >10 g/L or 2-3.5 gm loss/day	nephrotic syndrome or >3.5 gm loss/day
Hematuria	microscopic only	gross, no clots	gross + clots	obstructive or required transfusion
Cardiac Dysfunction				
Cardiac Rhythm	-	asymptomatic, transient signs, no Rx required	recurrent/persistent; no Rx required	requires Rx
Hypertension	transient inc. >20 mm; no Rx	recurrent, chronic, > 20 mm, Rx required	requires acute Rx; no hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; ECG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; >3 units transfused

^a Revised by the sponsor

Item	Grade 1	Grade 2	Grade 3	Grade 4
Respiratory				
Cough	transient; no Rx	treatment associated cough local Rx	uncontrolled	-
Bronchospasm, Acute	transient; no Rx <80-70% FEV ₁ (or peak flow)	requires Rx normalizes with bronchodilator; FEV ₁ 50-70% (or peak flow)	no normalization with bronchodilator; FEV ₁ 25-50% (or peak flow retractions)	cyanosis: FEV ₁ <25% (or peak flow) or intubated
Gastrointestinal				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/moderate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3-4 loose stools/day	5-7 loose stools/day	orthostatic hypotension or >7 loose stools/day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
Neuro & Neuromuscular				
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization
Neuro Control (ADL = activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minimal Rx	severe confusion/agitation needs assistance for ADL; therapy required	toxic psychosis; hospitalization
Muscle Strength	subjective weakness no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis

Item	Grade 1	Grade 2	Grade 3	Grade 4
Other Parameters				
Fever: oral, >12 hours	37.7-38.5 °C or 100.0-101.5 °F	38.6-39.5 °C or 101.6-102.9 °F	39.6-40.5 °C or 103-105 °F	>40.5 °C ^a or >105 °F
Headache	mild, no Rx	transient, moderate; Rx required	severe; responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25-50%	normal activity decreased >50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Local Reaction	tenderness or erythema	induration <10 cm or phlebitis or inflammation	induration >10 cm or ulceration	necrosis
Mucocutaneous ^a	erythema	diffuse, maculopapular rash, or dry desquamation	vesiculation, moist desquamation or ulceration, or any cutaneous event ^a	exfoliative dermatitis, mucous membrane involvement, erythema multiforme major, Stevens-Johnson Syndrome, or necrosis requiring surgery ^a

^a Revised by the sponsor

Attachment 2: Cardiovascular Safety – Abnormalities

The following abnormalities will be defined for vital sign measurements:

Abnormality Code	Vital Sign Parameters		
	Pulse	Diastolic Blood Pressure	Systolic Blood Pressure
Abnormalities on actual values			
Abnormally low	≤50 bpm	≤50 mmHg	≤90 mmHg
Grade 1 or mild	-	>90 mmHg to <100 mmHg	>140 mmHg to <160 mmHg
Grade 2 or moderate	-	≥100 mmHg to <110 mmHg	≥160 mmHg to <180 mmHg
Grade 3 or severe	-	≥110 mmHg	≥180 mmHg
Abnormally high	≥120 bpm	-	-

The classification of AEs related to hypotension and hypertension will be done according to the WHO Toxicity Grading Scale (see also [Attachment 1](#)).

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.

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 2 nd degree AV block OR Ventricular pause >3.0 sec	Complete AV block

*Revised by the sponsor.

Attachment 3: CLDQ-HCV Questionnaire

The aim of this questionnaire is to find out how you have been feeling during the last two weeks. You will be asked about symptoms related to your liver disease, how you have been affected in carrying out activities, and how your mood has been. Please answer all of the questions and select only **one** response for each question.

- 1. How often have you been tired or fatigued during the last 2 weeks?**
 - 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time

- 2. How much have you suffered from bodily pain over the last 2 weeks?**
 - 1 A very great deal of discomfort or pain
 - 2 A great deal of discomfort or pain
 - 3 A good deal of discomfort or pain
 - 4 A moderate amount of discomfort or pain
 - 5 Some discomfort or pain
 - 6 Very little discomfort or pain
 - 7 No discomfort or pain

- 3. How often during the last 2 weeks have you been restricted by your hepatitis C in performing your daily work (either at home or at work)?**
 - 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time

- 4. How much difficulty have you had with bending, lifting, or stooping in the last 2 weeks?**
 - 1 A very great deal of difficulty
 - 2 A great deal of difficulty
 - 3 A good deal of difficulty
 - 4 A moderate amount of difficulty
 - 5 Some difficulty
 - 6 Very little difficulty
 - 7 No difficulty

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- 5. How often during the last 2 weeks has your hepatitis C restricted your daily activities such as walking, climbing stairs, carrying shopping or participating in sports?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
- 6. How often during the last 2 weeks have you felt anxious?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
- 7. How often during the last 2 weeks have you felt a decreased level of energy?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
- 8. How often during the last 2 weeks have you felt cheerful or happy?**
- 1 None of the time
 - 2 Hardly any of the time
 - 3 A little of the time
 - 4 Some of the time
 - 5 Quite a lot of the time
 - 6 Most of the time
 - 7 All of the time
- 9. How often during the last 2 weeks have you felt irritable?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time

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10. **How often during the last 2 weeks have you had difficulty getting a refreshing sleep?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
11. **How often during the last 2 weeks have you had mood swings?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
12. **How often during the last 2 weeks have you had difficulty sleeping at night?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
13. **How often during the last 2 weeks have you had muscle cramps?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
14. **How often during the last 2 weeks have you been worried that your symptoms will develop into major problems?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time

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- 15. How often during the last 2 weeks have you felt that you may die earlier than expected because of your hepatitis C?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
- 16. How often during the last 2 weeks have you felt depressed?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
- 17. How often during the last 2 weeks have you been worried about your disease getting worse?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
- 18. How often during the last 2 weeks have you had problems with concentrating?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
- 19. How often during the last 2 weeks have you been worried about the effect your hepatitis C has on your family?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time

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20. How often during the last 2 weeks have you been concerned about the availability of a liver should you need a liver transplant?
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
21. How often during the last 2 weeks have you been concerned that you may transmit hepatitis C to your family, friends or work colleagues?
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
22. How often during the last 2 weeks have you been concerned that having hepatitis C would decrease your performance at work?
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
23. How often during the last 2 weeks have you felt uncomfortable in social situations?
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
24. How often during the last 2 weeks have you felt emotional strain or stress in your relationships because of hepatitis C?
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time

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- 25. How often during the last 2 weeks have you had a decreased interest in sex?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
- 26. How often during the last 2 weeks have you experienced pain in your joints?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
- 27. How often during the last 2 weeks have you felt discouraged because of your hepatitis C?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
- 28. How often during the last 2 weeks have you felt frustrated because of your hepatitis C?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time
- 29. How often during the last 2 weeks have you been concerned about the cost of your medication?**
- 1 All of the time
 - 2 Most of the time
 - 3 Quite a lot of the time
 - 4 Some of the time
 - 5 A little of the time
 - 6 Hardly any of the time
 - 7 None of the time

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Attachment 4: 5-level EuroQol 5-Dimension Questionnaire (EQ-5D-5L)



Health Questionnaire

English version for the USA

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Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

- I have no problems walking
- I have slight problems walking
- I have moderate problems walking
- I have severe problems walking
- I am unable to walk

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION

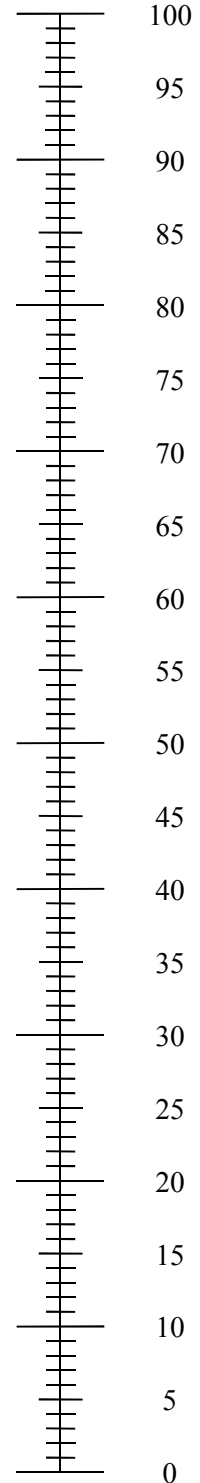
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

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- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine



The worst health
you can imagine

Attachment 5: Fatigue Severity Scale (FSS)

Below are a series of statements regarding your fatigue. By fatigue we mean a sense of tiredness, lack of energy or total body give-out. Please read each statement and choose a number from 1 to 7, where 1 indicates you completely disagree with the statement and 7 indicates you completely agree. Please answer these questions as they apply to the past TWO WEEKS.

	Completely disagree						Completely agree
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. My fatigue is very disabling.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family or social life.	1	2	3	4	5	6	7

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FSS - United States/English - Mapi Institute.
ID6492 / FSS_TS1.0_eng-USori.doc

Attachment 6: SF-36v2 Questionnaire

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....	<input type="checkbox"/> 1	<input checked="" type="checkbox"/> 2	<input type="checkbox"/> 3
c. Lifting or carrying groceries	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
d. Climbing <u>several</u> flights of stairs	<input checked="" type="checkbox"/> 1	<input checked="" type="checkbox"/> 2	<input type="checkbox"/> 3
e. Climbing <u>one</u> flight of stairs	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
f. Bending, kneeling, or stooping.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
g. Walking <u>more than a mile</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
h. Walking <u>several hundred yards</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
i. Walking <u>one hundred yards</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
j. Bathing or dressing yourself.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

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4. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the <u>amount of time</u> you spent on work or other activities.....	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input checked="" type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5
b. <u>Accomplished less than you</u> would like	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input checked="" type="checkbox"/> 4.....	<input type="checkbox"/> 5
c. Were limited in the <u>kind of</u> work or other activities.....	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5
d. Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort).....	<input checked="" type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5

5. During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the <u>amount of time</u> you spent on work or other activities.....	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5
b. <u>Accomplished less than you</u> would like	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5
c. Did work or other activities <u>less carefully than usual</u>	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5

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6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

7. How much bodily pain have you had during the past week?

None	Very mild	Mild	Moderate	Severe	Very severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input checked="" type="checkbox"/> 4	<input type="checkbox"/> 5
b. Have you been very nervous?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input checked="" type="checkbox"/> 4	<input type="checkbox"/> 5
c. Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input checked="" type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d. Have you felt calm and peaceful?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
e. Did you have a lot of energy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
f. Have you felt downhearted and depressed?	<input type="checkbox"/> 1	<input checked="" type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
g. Did you feel worn out?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
h. Have you been happy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
i. Did you feel tired?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b. I am as healthy as anybody I know	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c. I expect my health to get worse	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d. My health is excellent	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Thank you for completing these questions!

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Attachment 7: Visit Schedule for Rash Management

This visit schedule summarizes the visits and assessments to be performed in case of rash. At the investigator's discretion, additional visits and assessments can be performed. **Local laboratory blood sample assessments will be documented/collected as described in the text below.**

	Grade 1 Rash	Grade 2 Rash	Grade 3 or 4 Rash
Day 0^a	<ul style="list-style-type: none"> Study medication MAY be CONTINUED. Unscheduled visit (on-site) for initial rash evaluation may be performed at the investigator's discretion. Assessment of safety blood sample by local laboratory RECOMMENDED. 	<ul style="list-style-type: none"> Study medication MAY be CONTINUED. Unscheduled visit (on-site) for initial rash evaluation REQUIRED. If a visit is not possible, telephone contact with the subject should take place to collect information and to give advice on the necessary measures to be taken. Assessment of safety blood sample by local laboratory RECOMMENDED. Referral to dermatologist OPTIONAL (preferably within 24 hours after onset of rash, if performed). 	<ul style="list-style-type: none"> Grade 3: SMV MUST be permanently DISCONTINUED. AL-335 and ODV MAY be CONTINUED at the investigator's discretion. Close monitoring is REQUIRED to prevent progression of the rash. Grade 4: Study medication MUST be permanently DISCONTINUED. Rechallenge is NOT ALLOWED. Unscheduled visit for initial rash evaluation as soon as possible after the subject contacts the investigator to report the event REQUIRED. Assessment of safety blood sample by local laboratory REQUIRED. Referral to dermatologist REQUIRED (preferably within 24 hours after onset of rash). Biopsy REQUIRED for <u>grade 4</u> rash (as soon as possible after onset of rash). Biopsy at the dermatologist's discretion for grade 3 rash.
Day 1			<ul style="list-style-type: none"> Follow-up visit (on-site) REQUIRED. Assessment of safety blood sample by local laboratory REQUIRED.
Further Visits	<ul style="list-style-type: none"> Appropriate unscheduled follow-up visits at the investigator's discretion until resolution of rash.^b At these visits, safety blood samples can be taken at the investigator's discretion. 	<ul style="list-style-type: none"> Appropriate unscheduled follow-up visits at the investigator's discretion until resolution of rash.^b At these visits, safety blood samples must be taken. 	<ul style="list-style-type: none"> Appropriate follow-up REQUIRED until resolution of rash or until clinical stability is reached.

^a Note that Day 0 of the rash is the first day of Investigator assessment and not the first day of rash as reported by the subject.

^b In case rash progresses from a grade 1 or a grade 2 to a higher grade, start follow-up schedule for grade 2, 3 or 4 rash as appropriate.

Attachment 8: Anticipated Events**Anticipated Event**

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 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)

Reporting of Anticipated Events

These events will be captured in the CRF and in the database, and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any event that meets serious adverse event criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities, Investigators, and Independent Ethics Committee/Institutional Review Board. However, if based on an aggregate review it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Data Review Committee

A Data Review Committee (DRC) will be established in this study to perform reviews of pre-specified anticipated events at an aggregate level. The DRC is a committee within the sponsor's organization that is independent of the sponsor's study team. The DRC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events, will be included in the SAP.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): M. Biermer, MD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

LAST PAGE

SIGNATURES

Signed by

Rekha Sinha

Date

10Apr2017, 17:33:14 PM, UTC

Justification

Document Approval by Delegation