Janssen Pharmaceutical K.K.*

Clinical Protocol

A Phase 2a, Multicenter, Open-label Study to Investigate the Safety, Pharmacokinetics, and Efficacy of Combination Treatment of AL-335, Odalasvir, and Simeprevir in Japanese Subjects With Chronic Hepatitis C Genotype 1 or 2 Virus Infection, With or Without Compensated Cirrhosis who are Direct-acting Antiviral Treatment-naïve

Protocol 64294178HPC2003; Phase 2a
AMENDMENT 5
AL-335, odalasvir, TMC435 (simeprevir)

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	15 September 2016
Amendment 1	07 November 2016
Amendment 2	05 December 2016
Amendment 3	31 January 2017
Amendment 4	24 March 2017
Amendment 5	27 July 2017

Amendments below are listed beginning with the most recent amendment.

Amendment 5 (27 July 2017)

The overall reason for the amendment: This amendment is being written to increase monitoring of liver function tests based on ALT and AST elevation reported in Phase 2 studies.

Applicable Section(s)	Description of Change(s)
Rationale: To date, two similar cases of isolated, asymptomatic but marked ALT and AST elevation have been reported in the 3-DAA combination Phase 2 program (in 64294178HPC2003 and AL-335-604 study respectively). Approximately 470 subjects have already been exposed to 3-DAA combination in the Phase 2 program. Overall incidence of Grade 4 ALT elevation is 0.4% and its ALT/AST ratio is >1. No Grade 3 or Grade 4 ALT and AST elevations observed in 64294178HPC2001 study (N=365). Based on these laboratory abnormalities, sponsor decided to increase monitoring of liver function tests in 64294178HPC2003 study to weekly or biweekly instead of every 4 weeks during the treatment period.	
Time And Events Schedule 9.2.8.3. Alanine Aminotransferase, Aspartate Aminotransferase, and Bilirubin Elevations	Updated to add biochemistry tests including ALT and AST at on treatment Week 6 visit, and added the summary of observed ALT and AST abnormalities in Phase 2 program.

Amendment 4 (24 March 2017)

The overall reason for the amendment: This amendment is being written to implement study treatment stopping rules upon US Food and Drug Administration (FDA) feedback. In addition, changes are made to the definitions of on-treatment failure and relapse, and clarifications, corrections and updates are made in other section.

Applicable Section(s)	Description of Change(s)
Rationale: Following FDA 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 recruitment and dosing in all subjects in the study if adjudicated by the DRC to be at least possibly related to the study regimen. Such event(s) will be reported to the sponsor medical monitor within 24 hours. Upon this notification, a safety assessment of the event by the DRC will take place within 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.	

Applicable Section(s)	Description of Change(s)
1.3.2.2. Potential Risks 1.3.3. Overall Benefit/Risk Assessment 6.4. Study Treatment Stopping Rules 9.2.8.7. Cardiac Safety Monitoring 10.2. Discontinuation of Study Treatment/Withdrawal from the Study 11.9. Data Review Committee	Updated to add the treatment stopping rules.
Rationale: The definition of on-treatment failure and viral relapse are adjusted to align with FDA guidance on the development of direct-acting antivirals (DAAs) for the treatment of HCV infection.	
DEFINITIONS OF TERMS	The definition of on-treatment failure and viral relapse are adjusted.
Rationale: Minor errors and inconsistencies were corrected, and clarifications were added where required.	
TIME AND EVENTS SCHEDULE: RICH SERIAL PK ASSESSMENTS ABBREVIATIONS 9.2.8.6. Creatine Kinase 9.2.8.7. Cardiac Safety Monitoring	Minor errors and inconsistencies were corrected, and clarifications were added where required.

Amendment 3 (31 January 2017)

The overall reason for the amendment: In patients with compensated cirrhosis, based on preliminary data from Phase 2 study AL-335-604, suggesting further benefit, treatment durations of 8 and 12 weeks are studied in additional cohorts (Phase 2b). The outcome of this study will inform the duration evaluated in phase 3 for patients with compensated cirrhosis. To assess safety, PK and efficacy of the potentially longest treatment duration in Japanese subjects with compensated cirrhosis before going to phase 3, the Sponsor decided to extend the treatment duration of the cirrhotic cohort 2 in this study from 8 to 12 weeks.
In addition, clarifications, corrections and updates have been made in other sections, such as an update for the disallowed medication list, etc.

Applicable Section(s)	Description of Change(s)
Rationale: Extended treatment duration of Cohort 2 to 12 weeks from 8 weeks to assess the safety, PK and efficacy.	
Synopsis Objectives Overview Of Study Design Dosage And Administration 1.1.2. Treatment of HCV Infection 1.4. Overall Rationale for the Study 2.1.1. Objectives 3.1. Overview of Study Design 3.2. Study Design Rationale 6. Dosage And Administration 9.1.1. Overview 9.2.2. Clinical Laboratory Tests	Updated treatment duration for cohort 2 to 12 weeks and other related parts (eg. update of total study duration to 42 weeks from 38 weeks).
Rationale: Added an additional sparse PK sampling point for cohort 2 in accordance with the treatment extention.	

Applicable Section(s)	Description of Change(s)
Synopsis Pharmacokinetic Evaluations 3.1. Overview of Study Design 9.3.1. Evaluations	Added sparse PK sampling time point at Week 8 for cohort 2 and clarified description about the time points for each cohort.
Rationale: Updated Time and Events Schedule in accordance with the treatment extention for cohort 2, and added separated Time and Events Schedule for Week and Day of each visit schedule to show the required visit and day for each cohort at a glance.	
Time And Events Schedule Time And Events Schedule: Week/Day	Added Week 8 and 10 visit for cohort 2 and corresponding evaluations. Added separated Time and Events Schedule for Week and Day.
Rationale: Updated disallowed concomitant therapy and medication	
8. Prestudy And Concomitant Therapy	Added phlebotomy as disallowed concomitant therapy and clarified Prescription drugs for improvement of hepatic function which could potentially affect to hepatic function including AST and ALT as disallowed concomitant medication.
Rationale: Updated total blood volume to be drawn in this study in accordance with the treatment extention for cohort 2.	
9.1.1. Overview	Updated total blood volume to be drawn in this study in accordance with the treatment extention for cohort 2.
Rationale: Minor errors and inconsistencies were noted and corrected and clarifications were added where required.	
Time And Events Schedule Synopsis Data Review Committee 3.1. Overview of Study Design 4.2. Exclusion Criteria, #12 9.1.4. Posttreatment Period (Follow-up) 9.1.1. Overview 9.2.2. Clinical Laboratory Tests	Minor errors were corrected and clarifications were added.

Amendment 2 (05 December 2016)

The overall reason for the amendment: Following feedback and inquiries from Health Authority after submission of Clinical Trial Notification, the sponsor clarifies that dosing of cohort 2 will be started after no new or unexpected events, which are considered as clinically significant, are detected in cohort 1 regardless if the events are hepatotoxicity or not. In addition, clarifications, corrections and updates have been made in other sections, such as an update for subjects for whom an HBV DNA measurement is performed, clarifications for the disallowed medication list, etc.

Applicable Section(s)	Description of Change(s)
Rationale: Clarified dosing of cohort 2 will be started after no new or unexpected events, which are considered as a clinically significant, are detected regardless if the events are hepatotoxicity or not.	

Applicable Section(s)	Description of Change(s)
Synopsis Overview Of Study Design Data Review Committee 3.1. Overview of Study Design 9.1.1. Overview 11.9. Data Review Committee	Clarified dosing of cohort 2 will be started after no new or unexpected events, which are considered as a clinically significant, are detected regardless if the events are hepatotoxicity or not.
Rationale: Updated to perform HBV DNA measurement for subject with antiHBs positive status in addition to subjects with antiHBc positive status at screening, except for subjects with prior HBV-vaccinated and only antiHBs positive.	
Time And Events Schedule 9.1.3. Open-label Treatment Period 9.2.2. Clinical Laboratory Tests 9.2.6. Hepatitis B Virus DNA	Updated to perform HBV DNA measurement for subject with antiHBs positive status in addition to subjects with antiHBc positive status at screening, except for subjects with prior HBV-vaccinated and only antiHBs positive.
Rationale: Clarified the contraception methods not approved in Japan.	
4.1. Inclusion Criteria, #9 and 12	Clarified the contraception methods not approved in Japan.
Rationale: Clarified that the breast feeding female subjects cannot be enrolled even if they discontinue breast-feeding.	
4.2. Exclusion Criteria, #15	Clarified the criteria.
Rationale: Clarified the period of disallowed medications and added list of “Drugs associated with QT prolongation and/or Torsades de Pointes”.	
8. Prestudy And Concomitant Therapy, Table 1	Clarified that the period of disallowed medications and added list of “Drugs associated with QT prolongation and/or Torsades de Pointes”.
Rationale: Corrected the expected total blood volume drawn during the study.	
9.1.1. Overview	Corrected the expected total blood volume.
Rationale: Added representative ECG parameters as indices.	
9.2.3. Electrocardiogram	Added representative ECG parameters.
Rationale: Updated guidelines to discontinue all of study drugs in case of Grade 4 bilirubin elevation in light of securing subjects' safety.	
9.2.8.3. Alanine Aminotransferase, Aspartate Aminotransferase, and Bilirubin Elevations Table 7 10.2. Discontinuation of Study Treatment/Withdrawal from the Study	Updated guidelines for Grade 4 bilirubin elevation.
Rationale: Minor errors and inconsistencies were noted and corrected and clarifications were added where required.	

Applicable Section(s)	Description of Change(s)
Synopsis Overview Of Study Design 1.3.2.2. Potential Risks 1.3.3. Overall Benefit/Risk Assessment 3.1. Overview of Study Design 4.1. Inclusion Criteria, #9 9.1.3. Open-label Treatment Period 9.2.2. Clinical Laboratory Tests 9.2.4. Echocardiography 9.2.6. Hepatitis B Virus DNA 9.2.8.3. Alanine Aminotransferase, Aspartate Aminotransferase, and Bilirubin Elevations 11.9. Data Review Committee	Minor clarifications, grammatical and formatting changes were made.
9.2.3. Electrocardiogram	Minor errors were corrected.

Amendment 1 (07 November 2016)

The overall reason for the amendment: Change in design of the Phase 2a study with a staggered treatment fashion to start cohort 2 (chronic hepatitis C with compensated cirrhosis) after confirmation of tolerability in cohort 1 (chronic hepatitis C without cirrhosis), other clarification and minor updates.

Applicable Section(s)	Description of Change(s)
Rationale: Following Health Authority feedback, the sponsor has decided to start dosing in cohort 2 according to a DRC's decision after reviewing all available relevant safety data with 6 subjects until Week 4 visit in cohort 1, in light of securing subjects' safety. Dosing in cohort 2 will only be started when no new or unexpected signs or signals of hepatic toxicity, which are considered as a clinically significant issue, are detected. DRC may require further data to review before the decision about start of dosing in cohort 2, if any of potential concerns are detected with the data of 6 subjects until Week 4 visit in cohort 1. In addition, start of dosing in cohort 2 will be notified to investigators and be opened via an interactive web response system (IWRS) by the sponsor.	
Synopsis Overview Of Study Design Data Review Committee 9.1.1. Overview 11.9. Data Review Committee	Added description about DRC review for decision to start dosing in cohort 2, notification of start of dosing in cohort 2.
3.1. Overview of Study Design	Added description about DRC review for decision to start dosing in cohort 2. Updated Figure 1 (Schematic Overview of the Study) to show the updated study design visually.
Rationale: Description related to anticipated events were removed as they will not be identified for Japanese Health Authority.	

Applicable Section(s)	Description of Change(s)
Synopsis Overview Of Study Design Data Review Committee 1.3.3. Overall Benefit/Risk Assessment 3.1. Overview of Study Design 9.1.3. Open-label Treatment Period 9.2. Safety Evaluations 11.9. Data Review Committee 12.3.1. All Adverse Events Attachment 4: Anticipated Events	Description related to anticipated events were removed.
Rationale: Requirement for dosage and administration of study drugs were clarified for each subgroup, sparse PK and rich PK substudies.	
6. Dosage And Administration 7. Treatment Compliance	Clarified the requirement for each subgroup.
Rationale: Clarified the required period for use of birth control.	
4.1. Inclusion Criteria	Clarified the required period for use of birth control under inclusion criteria #9 and 12.
Rationale: Added new definition of term, Late viral relapse.	
Definitions Of Terms	Added new definition of term, Late viral relapse.
Rationale: Minor errors and inconsistencies were noted and corrected and clarifications were added where required.	
Synopsis Time And Events Schedule 1.3.3. Overall Benefit/Risk Assessment 3.1. Overview of Study Design 6. Dosage And Administration 9.1.2. Screening Period 9.3.3. Pharmacokinetic Parameters	Minor grammatical and formatting changes were made.
4.1. Inclusion Criteria, #11 9.1.1. Overview 9.2.2. Clinical Laboratory Tests 9.2.8.1. Rash (Including Photosensitivity Conditions) 9.3.1. Evaluations 9.5.1. HCV RNA Levels	Minor errors were corrected.

SYNOPSIS

A Phase 2a, Multicenter, Open-label Study to Investigate the Safety, Pharmacokinetics, and Efficacy of Combination Treatment of AL-335, Odalasvir, and Simeprevir in Japanese Subjects With Chronic Hepatitis C Genotype 1 or 2 Virus Infection, With or Without Compensated Cirrhosis who are Direct-acting Antiviral Treatment-naïve

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

Odalasvir (ODV, JNJ-64289901, also known as ACH-0143102 and ACH-3102) is an inhibitor of the HCV NS5A complex, being developed for the treatment of chronic HCV infection.

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

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Objectives

Primary Objectives

- To evaluate the safety and tolerability of a combination treatment of AL-335, ODV, and SMV for 8 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection without cirrhosis and for 12 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection with compensated cirrhosis.

Secondary Objectives

- To evaluate the pharmacokinetics (PK) of AL-335 (and its 2 metabolites ALS-022399 and ALS-022227; AL-335, the metabolites ALS-022399 and ALS-022227 are hereafter referred to as AL-335 [and metabolites]), ODV, and SMV in plasma in Japanese subjects with genotype 1 or 2 chronic HCV infection with or without compensated cirrhosis who are DAA-naïve.
- To evaluate the efficacy, ie, sustained virologic response (SVR) at 4, 12, and 24 weeks after the end-of-treatment (EOT) (SVR4, SVR12, and SVR24), of a combination treatment with AL-335, ODV, and SMV for 8 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection without cirrhosis and for 12 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection with compensated cirrhosis.
- To evaluate on-treatment viral kinetics in an 8 or 12-week treatment regimen containing AL-335, ODV, and SMV in subjects who are DAA- naïve.
- To evaluate the incidence of on-treatment failure during an 8 or 12-week treatment regimen containing AL-335, ODV, and SMV in subjects who are DAA-naïve.
- To evaluate the incidence of viral relapse after an 8 or 12-week treatment regimen containing AL-335, ODV, and SMV in subjects who are DAA-naïve.

Exploratory Objectives

- To explore relationships of exposure of AL-335 (and metabolites), ODV, and SMV with SVR and safety.
- To evaluate the impact of the patient and disease characteristics at baseline on SVR, including but not limited to prior treatment history, interleukin-28B (*IL28B*) genotype, presence of cirrhosis, HCV RNA level, and HCV geno/subtype.

- To evaluate the impact of the presence of HCV NS3/4A, NS5A, and/or NS5B polymorphisms at baseline on treatment outcome.
- To assess the emergence of resistant variants in subjects not achieving SVR.

Endpoints

Primary Endpoint

- Safety data, including but not limited to adverse events (AEs), physical examination, vital signs, 12-lead electrocardiograms (ECGs), echocardiograms, and clinical laboratory results (including chemistry, hematology, and urine)

Secondary Endpoints

- PK parameters for AL-335 (and metabolites), ODV, and SMV in plasma
- The proportion of subjects who have an SVR4, SVR12, and SVR24
- The proportion of subjects with viral relapse
- The proportion of subjects with on-treatment failure
- The proportion of subjects with on-treatment virologic response:
  - HCV RNA not detected
  - HCV RNA <lower limit of quantification (LLOQ)
- Time to achieve HCV RNA not detected or HCV RNA <LLOQ

Exploratory Endpoints

- The effect of the presence or absence at baseline of HCV NS5A, NS5B, and/or NS3/4A polymorphisms on treatment outcome
- The changes in the HCV NS3/4A, NS5A and/or NS5B sequences in subjects not achieving SVR
- Impact of baseline condition on SVR (including but not limited to prior treatment history, *IL28B* genotype, presence of cirrhosis, HCV RNA level, and HCV geno/subtype)

Hypothesis

The study is hypothesis-generating. No formal hypothesis will be tested.

OVERVIEW OF STUDY DESIGN

This is a Phase 2a, multicenter, open-label study to investigate the safety, efficacy, and PK of an 8 or 12-week treatment regimen with AL-335, ODV, and SMV in Japanese subjects with genotype 1 or 2 chronic HCV infection with or without compensated cirrhosis who are DAA-naïve, followed by a 24-week posttreatment follow-up.

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 Period can be extended if discussed with and approved (documented) by the sponsor. Thereafter, if eligible, subjects will be assigned to 1 of the 2 treatment cohorts to receive AL-335, ODV, and SMV combination treatment for 8 or 12 weeks based on the absence or presence of compensated cirrhosis. A posttreatment follow-up until 24 weeks after the actual EOT is included to assess SVR4, SVR12, and SVR24. The total study duration for each subject will be approximately 38 or 42 weeks (including the 6-week Screening Period, the 8 or 12-week

Treatment Period, and the 24-week Posttreatment Follow-up Period). The study will be considered to be completed with the last visit of the last subject participating in the study.

Approximately 20 DAA-naïve chronic HCV genotype 1 or 2-infected subjects without cirrhosis will be assigned to Cohort 1, and approximately 20 DAA-naïve HCV genotype 1 or 2-infected subjects with compensated cirrhosis will be assigned to Cohort 2.

- Cohort 1 (N=20, chronic hepatitis C without cirrhosis): AL-335 800 mg once daily (qd) + ODV 25 mg qd + SMV 75 mg qd for 8 weeks
- Cohort 2 (N=20, chronic hepatitis C with compensated cirrhosis): AL-335 800 mg qd + ODV 25 mg qd + SMV 75 mg qd for 12 weeks

Subjects volunteering to participate, having signed the informed consent form (ICF), and found eligible for the study at screening, will be required to discontinue specified disallowed medication.

The primary objective of this study is to assess safety and tolerability of the 3 DAA combination in Japanese patients with and without compensated liver cirrhosis. Compared to subjects with chronic hepatitis C without cirrhosis (enrolled in cohort 1), subjects with chronic hepatitis C with compensated cirrhosis (enrolled in cohort 2) are considered to potentially have a higher safety risk. To conduct this study carefully in light of securing subjects' safety, dosing of cohort 2 with patients with compensated cirrhosis will only start after a Data Review Committee (DRC) has reviewed all available relevant safety data when the first 6 subjects in cohort 1 completed the Week 4 visit, (including but not limited to AE, Serious AE [SAE], clinical laboratory test) and no new or unexpected events, which are considered clinically significant, are detected. DRC may require to review data of further patients before deciding about the start of dosing in cohort 2.

If study drug 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. If a subject discontinues treatment due to withdrawal of consent, the subject will be offered an optional 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 Visit need to be performed.

Subjects will discontinue study drugs if a virologic 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 increase of >1.0 $\log_{10}$ IU/mL in HCV RNA from nadir or confirmed HCV RNA >2.0 $\log_{10}$ IU/mL in subjects who had previously achieved HCV RNA <LLOQ (detected or not detected) while on treatment.

DRC will be established to monitor data with focus on the safety and on the general conduct of the study. The DRC is a committee within the sponsor’s organization that is independent of the sponsor’s study team. Details will be specified in a separate charter.

SUBJECT POPULATION

Key Inclusion Criteria	Description
Age and sex	Man or woman, 20 to 75 years of age, inclusive.
Body Mass Index	Body mass index of 18.0 to 35.0 kg/m^2, inclusive.
HCV genotype	All subjects must have HCV genotype 1 or 2 infection, determined at screening.
Plasma HCV RNA	≥10,000 IU/mL (determined at screening).
HCV treatment history	Subjects must be DAA-naïve, defined as not having received treatment with any approved or investigational DAA for chronic HCV infection. Prior HCV therapy consisting of interferon (IFN) (pegylated or nonpegylated) with or without ribavirin (RBV) is allowed.
Presence or absence of cirrhosis	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). Subjects with compensated cirrhosis (not meeting the criterion for hepatic decompensation described in the Exclusion Criteria), defined as any of the following: • Fibroscan (prior report or during Screening Period) with a result of >12.5 kPA, OR • Liver biopsy (prior report or during Screening Period) showing cirrhosis (eg, METAVIR score of F4 or Ishak score ≥5).

Key Exclusion Criteria	Description
Infection/coinfection	HCV coinfection with multiple genotypes. Human immunodeficiency virus (HIV) coinfection. HCV genotype 3, 4, 5, or 6 infection.
Exposure to a DAA	Prior exposure to an HCV DAA, either in combination with pegylated interferon (PegIFN) or IFN-free.
Liver disease of nonHCV etiology	Any evidence of liver disease of nonHCV etiology. This includes, but is not limited to, acute hepatitis A infection (immunoglobulin M), hepatitis B infection (hepatitis B surface antigen [HBsAg] positive), drug- or alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, primary biliary cirrhosis, or any other nonHCV 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, hair transplant, or skin graft).

Cardiac-related medical history	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) <55.0% or any other echocardiogram finding suggestive of clinically relevant cardiomyopathy • abnormal ECG findings such as: significantly abnormal PR [PR interval >200 msec], QRS intervals or corrected QT interval [QTc] >450 msec for male subjects and >470 msec for female subjects (based on the average of the ECGs) • evidence of any heart block • evidence of right bundle branch block or left bundle branch block • history or family history of prolonged QT syndrome (eg, torsade de pointes) or sudden cardiac death
Key laboratory values	Any of the following laboratory abnormalities at screening: • platelet count $<75\times10^3/\mu L$ or $<75\times10^9/L$ • hemoglobin <11 g/dL or <6.83 mmol/L for male subjects, <10 g/dL or <6.21 mmol/L for female subjects • absolute neutrophil count $<1.00\times10^3/\mu L$ • alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >10×upper limit of normal (ULN) • total serum bilirubin >1.5×ULN • albumin <3.5 g/dL or <35 g/L • estimated glomerular filtration rate (eGFR) of <50 mL/min/1.73m^2 • hypo-/hyperkalemia (Grade 2 or higher)
Hepatocellular carcinoma	Subjects who have a history of hepatocellular carcinoma regardless of period before screening; or currently, 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. The treatment duration is 8 weeks for subjects without cirrhosis (cohort 1) and 12 weeks for subjects with compensated cirrhosis (cohort 2).

All study drugs should be taken together in the morning at approximately the same time with food (ie, during or within 15 minutes after completion of a meal).

SAFETY EVALUATIONS

Safety and tolerability will be evaluated throughout the study from signing of the ICF onwards until the subject's last study visit. The evaluations of safety and tolerability will include monitoring of AEs, clinical laboratory tests, ECGs, echocardiograms, vital sign measurements, and physical examinations at predefined time points.

All AEs, whether serious or nonserious 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 pharmacologic profile of the study drugs (and the drug class) evaluated in this study are incorporated in this protocol.

PHARMACOKINETIC EVALUATIONS

Sparse PK Sampling

Sparse PK sampling for the measurement of plasma concentrations of AL-335 (and metabolites), ODV, and SMV will be performed in all subjects. Sparse PK sample will be taken at predose, between 2-to 4-hours postdose, and between 4- to 6-hours postdose at Weeks 2, 4, 6 and at the EOT (Week 8) Visit (Cohort 1), or Weeks 2, 4, 6, 8 and at the EOT (Week 12) Visit (Cohort 2). At Week 4, no sparse PK sample will be taken for subjects participating in the rich serial PK substudy. At the Week 12 Follow-up Visit, sparse PK sample will be taken at any time for the measurement of plasma concentrations of ODV. Study drugs should be taken on site at the time points in the Time and Events Schedule.

Rich Serial PK Sampling for Noncompartmental PK Analysis in the PK Subgroups

In the rich serial PK substudy, rich serial PK blood sampling for the measurement of plasma concentrations of AL-335 (and metabolites), ODV, and SMV will be performed in approximately more than 6 subjects in each cohort. 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. For the intensive PK samples of the rich PK substudy, noncompartmental PK analysis of AL-335 (and metabolites), ODV, and SMV will be performed using actual sampling time points and plasma concentrations obtained from rich serial PK blood sampling at Week 4.

EFFICACY EVALUATIONS

HCV RNA Levels

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

Resistance Determinations

Sequencing of the HCV NS3/4A, NS5A, and NS5B regions will be performed to identify preexisting sequence polymorphisms and characterize emerging HCV variants. The HCV NS3/4A, NS5A, and NS5B regions will be sequenced pretreatment (at baseline) by default in all subjects and postbaseline in subjects not achieving SVR. Sequencing of additional samples may be triggered by the sponsor's virologist.

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. No other analysis will be performed with this sample.

Determination of the subject's *IL28* genotype will be performed on human genomic deoxyribonucleic acid (DNA) by techniques allowing amplification of the DNA and identification of the polymorphism.

STATISTICAL METHODS

Sample Size Determination

Since this is an exploratory study, no formal sample size calculation has been performed.

With a total sample size of 40 subjects, the probability to observe an AE with an incidence of 10.0% is 99.0%. The probability to observe an AE with an incidence of 1.0%, 2.5%, and 5.0% is 33.0%, 64.0%, and 87.0%, respectively. With 20 subjects per cohort, the probability to observe an AE with an incidence of 10.0% is 88.0%. The probability to observe an AE with an incidence of 1.0%, 2.5%, and 5.0% is 18.0%, 40.0%, and 64.0%, respectively in a cohort.

With an expected SVR rate of 90.0%, and 40 subjects in 2 cohorts combined, the corresponding 95%, 2-sided confidence interval (CI) is 76.3% to 97.2%. With 95.0% SVR, the corresponding 95% CI ranges from 83.1% to 99.4%. With an expected SVR rate of 90.0%, and 20 subjects per cohort, the corresponding 95%, 2-sided CI is 68.3% to 98.8%. With 95.0% SVR, the corresponding 95% CI ranges from 75.1% to 99.9% in a cohort.

Therefore, a total sample size of approximately 40 subjects is considered sufficient to explore the safety and efficacy of the combination regimen consisting of AL-335, ODV, and SMV in this study from a clinical point of view.

Interim Analysis

No formal interim analysis will be performed; however, a DRC will be commissioned to regularly monitor the safety in interim data review.

Safety Analyses

The incidence of AEs will be summarized by body system and preferred term for each cohort and total. Changes from baseline in clinical laboratory values, vital signs, and ECG parameters will be presented descriptively. The percentage of subjects with abnormal clinical laboratory, vital signs, and ECG parameter values will be presented.

The safety analyses will be done separately for each study period (screening, treatment, and follow-up).

Pharmacokinetic Analyses

Population PK Analysis for all Subjects

Population PK (PopPK) analysis of plasma concentration-time data of AL-335 (and metabolites), ODV, and SMV from all subjects will be performed using nonlinear mixed-effects modeling. PopPK 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. For each cohort, descriptive statistics, including arithmetic mean, standard deviation (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 metabolites), ODV, and SMV.

Rich Serial PK Sampling for Noncompartmental PK Analysis in the PK Subgroups

For each cohort, descriptive statistics will be provided for the plasma concentrations at each sampling time point and the PK parameters derived.

All individual concentrations at each sampling time point and all individual PK parameters will be listed. For each subject, plasma concentration-time data will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. PK parameters will be subjected to an exploratory graphical analysis. Additional analyses may be performed if deemed warranted.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships of AL-335 (and metabolites), ODV, and SMV population-derived exposure parameters (AUC_{24h} and C_{0h}) with SVR4, SVR12, and SVR24 and with safety endpoints may be explored. These relationships will be presented in a graphical display.

Efficacy Analyses

The primary analyses will be performed when all subjects have reached the SVR12 time point (Week 12 Follow-up Visit) or discontinued earlier. The final analysis (as secondary analysis) will be performed when all subjects have completed the last study-related visit (SVR24 time point; Week 24 Follow-up Visit) or discontinued earlier.

The efficacy analyses will be performed on the full analysis set (FAS), defined as all subjects who received at least 1 dose of the study drug (AL-335, ODV, or SMV) and have at least 1 postbaseline efficacy measurement in the current study. Additional sensitivity analyses on efficacy may be performed after excluding subjects with early treatment discontinuation due to nonvirologic reasons or missing data at SVR4, SVR12, or SVR24 time points, as well as on the per-protocol set (PPS), defined as the FAS subjects without a prespecified major protocol deviation.

The potential association between treatment outcome and baseline subject and disease characteristics such as prior treatment history, *IL28B* genotype (rs12979860), presence of cirrhosis, HCV RNA level, and HCV geno/subtype will be explored.

Criteria for Endpoints

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.

Resistance Determination Analyses

Pretreatment 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 pretreatment HCV NS3/4A, NS5A, and NS5B polymorphisms on treatment outcome will be explored.

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.

Data Review Committee

A DRC will be established to monitor data with focus on the safety and generally on the conduct of the study. Emerging safety data from this study will be reviewed at predetermined intervals.

To conduct this study carefully in light of securing subjects' safety, dosing of cohort 2 with patients with compensated cirrhosis will only start after a DRC has reviewed all available relevant safety data when the first 6 subjects in cohort 1 completed the Week 4 visit, (including but not limited to AE, SAE, clinical laboratory test) and no new or unexpected events, which are considered clinically significant, are detected. DRC may require to review data of further patients before deciding about the start of dosing in cohort 2.

TIME AND EVENTS SCHEDULE

Period	Screening Period[a]	Treatment Period[c]												Posttreatment Follow-up Period				
Week/Day	**W-6**	**Baseline[b] D1**	**D2**	**D3**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8[ff]**	**W10[ff]**	**EOT (W8 or 12)[gg]**	**Treatment Withdrawal Visit[d]**	**W4 FU**	**W8 FU**	**W12 FU**	**W18 FU**	**W24 FU[e]**
Study Procedures																		
Screening/Administrative																		
Informed consent form[f]	X																	
Demographics	X																	
Medical/surgical history	X																	
Prestudy therapies	X																	
Concomitant diseases	X																	
Inclusion/exclusion criteria	X	X[g]																
Hepatitis C virus geno-/subtyping	X																	
Fibroscan/biopsy[h]	X																	
Liver ultrasonography, CT, or MRI[aa] (subjects with cirrhosis)	X																	
Echocardiography[i]	X							X				X	X	X				
Triplicate ECG[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Pregnancy test[j]	X	X						X		X		X	X	X	X	X	X	X
Follicle-stimulating hormone (FSH)[k]	X																	
Hepatitis A, B, and C serology	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[ee]		X[ee]								
Study drugs to be taken on-site		X				X		X	X	X		X						

Period	Screening Period[a]	Treatment Period[c]												Posttreatment Follow-up Period				
Week/Day	**W-6**	**Baseline[b] D1**	**D2**	**D3**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8[ff]**	**W10[ff]**	**EOT (W8 or 12)[gg]**	**Treatment Withdrawal Visit[d]**	**W4 FU**	**W8 FU**	**W12 FU**	**W18 FU**	**W24 FU[e]**
Study Procedures																		
Provision and explanation 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					
Adherence counseling		X	X	X	X	X	X	X	X	X	X	X						
Efficacy Assessments																		
HCV RNA determination[m]	X	X[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Viral sequencing[n]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics																		
Sparse PK - plasma concentrations of AL-335 (and metabolites), ODV and SMV[o]						X[p,s]		X[p,r,s]	X[p,s]	X[p,s]		X[p,s]				X[q]		
Rich PK substudy - plasma concentrations of AL-335 (and metabolites), ODV, and SMV					See TIME AND EVENTS SCHEDULE: Rich serial PK Assessments													
Safety Assessments																		
Physical examination[t]	X	X			X	X		X		X		X	X	X				X
Vital signs[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X
Clinical Laboratory Assessments																		
Hematology, biochemistry	X[x]	X[v,w,bb]			X	X[v,bb]		X[v,bb]	X[bb]	X[bb]	X[bb]	X[v,w,x,bb]	X[x]	X[v,bb]	X[dd]	X[v,w]	X[dd]	X
Urinalysis	X[y]	X			X	X		X		X		X	X	X		X		X
HBV DNA[cc]												X	X					
Pharmacogenomics (blood sample)																		
Host interleukin-28B (*IL28B*) genotyping		X																

Period	Screening Period[a]	Treatment Period[c]												Posttreatment Follow-up Period				
Week/Day	**W-6**	**Baseline[b] D1**	**D2**	**D3**	**W1**	**W2**	**W3**	**W4**	**W6**	**W8[ff]**	**W10[ff]**	**EOT (W8 or 12)[gg]**	**Treatment Withdrawal Visit[d]**	**W4 FU**	**W8 FU**	**W12 FU**	**W18 FU**	**W24 FU[e]**
Study Procedures																		
Ongoing Subject Review																		
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CT=computed tomography; BNP=B-type natriuretic peptide; D=day(s); DNA=deoxyribonucleic nucleic acid; ECG=electrocardiogram; EOT=end-of-treatment; ICF=informed consent form; LLOQ=lower limit of quantification; HBV=hepatitis B virus; antiHBc=hepatitis B core antibody; HCV=hepatitis C virus; FU: follow-up; MRI= magnetic resonance imaging; ODV=odalasvir; PK=pharmacokinetic; RNA=ribonucleic acid; SMV=simeprevir; TSH= thyroid stimulating hormone; W=week

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 Period to assess eligibility. Any potential delays in the Screening Period 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.

c. Subjects should ensure intake of study drugs up to 8 weeks (56 ± 1 days) or 12 weeks (84 ± 1 days) of treatment, in order to complete the indicated treatment duration. A Data Review Committee (DRC) will be established in this study to perform reviews with focus on the safety.

d. If study drug 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 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.

e. Any subject who withdraws consent during the Follow-up Period and/or notifies the site that 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.

f. Signing of the ICF can be done before the Screening Visit but needs to be done before the first study-related activity.

g. Investigator to confirm eligibility based on the overall clinical picture.

h. In subjects with cirrhosis, cirrhosis confirmed by a fibroscan or liver biopsy performed prior to or during the Screening Period. For subjects without cirrhosis, absence of cirrhosis confirmed by fibroscan performed or liver biopsy within 6 months of baseline (Day 1).

i. Additional ECG or echocardiography 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.

j. 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 or 6 weeks up to the W24 FU Visit.
k. Follicle-stimulating hormone will be tested for female subjects who are postmenopausal for less than 2 years.
l. A blood sample needs to be taken at predose. The timing of the predose blood sample, as well as the timing of the dosing at baseline should be recorded.
m. During follow-up, suspected relapse, ie, HCV RNA ≥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.
n. Viral sequencing will be performed at baseline by default in all subjects and at postbaseline in subjects not achieving sustained virologic response (SVR). Sequencing of additional samples may be triggered by the sponsor virologist.
o. Sparse PK sampling for AL-335 (and metabolites), ODV, and SMV will be performed in all subjects.
p. Sparse PK sample will be taken at predose, between 2 to 4-hours postdose, and between 4- to 6-hours postdose. Study drugs should be taken on site.
q. Sparse PK sample will be taken any time during the visit for ODV only.
r. No sparse PK sample will be taken for subjects participating in the rich serial PK substudy.
s. Intake of study drugs should take place on site when predose PK sampling is performed.
t. 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.
u. Systolic and diastolic blood pressure and pulse rate need to be taken supine after at least 5 minutes of rest.
v. Biochemistry samples must be taken after fasting for at least 8 hours at these visits as the lipid profile is also assessed.
w. An additional blood sample for biochemistry should be taken for assessment of insulin and glucose after fasting for at least 8 hours.
x. Thyroid stimulating hormone (TSH) is to be assessed at screening and EOT or early withdrawal.
y. Includes a urine drug screening test.
z. All adverse events (AEs), whether serious or nonserious, and pregnancies will be reported from the time a signed ICF is obtained until the subject's last study visit.
aa. Subjects with cirrhosis have to receive an ultrasound scan, computed tomography (CT) scan, or magnetic resonance imaging (MRI) within 3 months prior to baseline/Day 1.
bb. Includes assessment of B-type natriuretic peptide (BNP).
cc. HBV DNA will be evaluated at the EOT Visit, or Treatment Withdrawal Visit, and may be evaluated at any time when there is a significant increase in the AST or ALT levels. This only refers to subjects with antiHBc and/or HBs antibody [antiHBs] positive status at screening and not to subjects who have received HBV vaccine and are only antiHBs positive.
dd. Serum chemistry panel only, excluding TSH, BNP, glucose, insulin, and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol.
ee. Provision of study drug at Week 4 (all subjects) and 8 (Cohort 2 only) in principal.
ff. Only for subjects enrolled in Cohort 2.
gg. Week 8 (D56) for subjects enrolled in Cohort 1, and Week 12 (D84) for subjects enrolled in Cohort 2.

TIME AND EVENTS SCHEDULE: WEEK/DAY AND TIME WINDOWS

Period		Screening Period	Treatment Period												Posttreatment Follow-up Period				
Week/ Day	Cohort 1	W-6	Baseline D1	D2	D3	W1 (D7)	W2 (D14)	W3 (D21)	W4 (D28)	W6 (D42)	-	-	EOT (D56)	Treatment Withdrawal Visit	W4 FU (D84)	W8 FU (D112)	W12 FU (D140)	W18 FU (D182)	W24 FU (D224)
		(D-42 to D0)				-1 to + 1D (D6 to D8)	-2 to + 2D (D12 to D16)	-2 to + 2D (D19 to D23)	-2 to + 2D (D26 to D30)	-2 to + 2D (D40 to D44)	-	-	-1 to + 1D (D55 to D57)		-3 to + 3D (D81 to D87)	-7 to + 7D (D105 to D119)	-7 to + 7D (D133 to D147)	-7 to + 7D (D175 to D189)	-7 to + 7D (D217 to D231)
	Cohort 2	W-6	Baseline D1	D2	D3	W1 (D7)	W2 (D14)	W3 (D21)	W4 (D28)	W6 (D42)	W8 (D56)	W10 (D70)	EOT (D84)	Treatment Withdrawal Visit	W4 FU (D112)	W8 FU (D140)	W12 FU (D168)	W18 FU (D210)	W24 FU (D252)
		(D-42 to D0)				-1 to + 1D (D6 to D8)	-2 to + 2D (D12 to D16)	-2 to + 2D (D19 to D23)	-2 to + 2D (D26 to D30)	-2 to + 2D (D40 to D44)	-2 to + 2D (D54 to D58)	-2 to + 2D (D68 to D72)	-1 to + 1D (D83 to D85)		-3 to + 3D (D109 to D115)	-7 to + 7D (D133 to D147)	-7 to + 7D (D161 to D175)	-7 to + 7D (D203 to D217)	-7 to + 7D (D245 to D259)

TIME AND EVENTS SCHEDULE: RICH SERIAL PK ASSESSMENTS

Rich Serial PK Substudy[a] (Approximately More Than 6 Subjects in Each Cohort[b])

Time of Visit	Sampling Time (hours)										
	Predose	Dosing	1 h	2 h	3 h	4 h	6 h	8 h	10 h	12 h	24 h
Week 4[c]	X[d]		X	X	X	X	X	X	X	X	X[e]

Key: h=hour(s); ODV=odalasvir; PK=pharmacokinetic; SMV=simeprevir

a. This may require an overnight stay in the hospital.
b. Rich PK sampling for AL-335 (and metabolites), ODV, and SMV will be performed in approximately more than 12 subjects (Cohorts 1 and 2 combined).
c. Study drugs should be taken on site.
d. The predose sample should be collected before study drug intake (within 0.5 hour before).
e. The 24 hour PK sample must be taken before study drug intake on the morning following the overnight stay.

ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
antiHBc	hepatitis B core antibody
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24h}	AUC from time 0 to 24 hours
AV	atrioventricular
C_{0h}	predose plasma concentration
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase muscle-brain
C_{max}	maximum drug concentration
C_{min}	minimum plasma concentration
CT	computed tomography
CYP	cytochrome P450
DAA	direct-acting antiviral
DCV	daclatasvir
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DRC	Data Review Committee
EC_{50}	50% effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EOT	end-of-treatment
FAS	full analysis set
FC	fold change
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IL	interleukin
IWRS	interactive web response system
IRB	Institutional Review Board
IUS	intrauterine hormone-releasing system
LFC	liquid-filled capsule
LLOQ	lower limit of quantification
LVEF	left ventricular ejection fraction
MAD	multiple ascending dose
MRI	magnetic resonance imaging
MRP	multidrug resistance-associated protein
NS	nonstructural protein
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
ODV	odalasvir

PD	pharmacodynamic
PegIFN	pegylated interferon
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
popPK	population PK
PQC	product quality complaint
qd	once daily
qod	once every other day
QTc	corrected QT interval
QTcF	QT corrected according to Fredericia's formula
RAV	resistance-associated variants
RBC	red blood cell
RBV	ribavirin
RGT	response-guided therapy
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SMV	simeprevir
SOF	sofosbuvir
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
$t_{1/2,term}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach the maximum plasma concentration
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

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 not detected or HCV RNA <lower limit of quantification (LLOQ) (detected or not detected) at specified time points during treatment.
Sustained Virologic Response (SVR*X*)	Subjects achieve SVR*X* if HCV RNA <LLOQ (detected or not detected) *X* weeks after the actual EOT.
Failure (no SVR12)	Subjects who do not achieve SVR12, including: on-treatment failure (see below) posttreatment failure, including subjects with: - 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 ≥LLOQ at the actual EOT. Includes subjects with: - viral breakthrough, defined as a confirmed increase of >1.0 $\log_{10}$ IU/mL in HCV RNA from nadir or confirmed HCV RNA >2.0 $\log_{10}$ IU/mL in subjects who had previously achieved HCV RNA <LLOQ (detected or not detected) while on treatment. - other with confirmed HCV RNA ≥LLOQ 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 ≥LLOQ during follow-up.
Late viral relapse	Subjects who achieved SVR12 but have confirmed HCV RNA ≥LLOQ afterwards during follow-up (after W12 FU, and before or at W24 FU visit).

1. INTRODUCTION

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

Odalasvir (ODV, JNJ-64289901, also known as ACH-0143102 and ACH-3102) is an inhibitor of the HCV NS5A complex, being developed for the treatment of chronic HCV infection.

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

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, for AL-335,[16,18] ODV,[19,20] and SMV.[21,22]

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

Hepatitis C virus infection is a leading cause of liver disease worldwide. An estimated 130 to 150 million people (about 2.0% of the global population) are currently infected with HCV,[36] with an incidence of 3 to 4 million new infections per year.[37] Between 70.0% and 90.0% of acute HCV infections become chronic and may lead to liver cirrhosis, chronic liver failure, hepatocellular carcinoma, liver transplantation, and death.[8,25,37] Complications of HCV infection are currently the most common indication for liver transplantation. In the US 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.[7] The risk of hepatic decompensation in subjects with cirrhosis is approximately 5.0% per year and the 5-year survival rate after decompensation is around 50.0%.[4]

Hepatitis C virus has been classified into at least 6 major genotypes (designated 1 to 6) and many subtypes (a, b, c, etc).[7] 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 (46.0%), followed by genotype 3 (30.0%), genotype 2 (9.0%), genotype 4 (8.0%), genotype 6 (5.0%), and genotype 5 (<1.0%).[27] Genotype 1b is the most common subtype, accounting for 22.0% of all infections. Infections in North America, Latin America, and Europe are predominantly of genotype 1. North Africa and the Middle East were found to have a large genotype 4 population (71.0%), which is related to the high prevalence of genotype 4 in Egypt.

Asia has predominantly genotype 3 (39.0%), largely driven by the HCV infections in India and Pakistan, followed by genotype 1 (36.0%).[12]

In Japan, the number of patients with chronic Hepatitis C viremia is estimated to be 1.5 to 2 million. The distribution of HCV genotype 1b, 2a, and 2b was reported as 70%, 20%, and 10%, respectively. Almost all of HCV genotype 1 in Japan is of the 1b subtype.[30]

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.[28,29,32] Since 2014, additional DAAs, including daclatasvir (DCV) (Daklinza®),[6] dasabuvir (Exviera®)[9] and the fixed-dose combinations SOF/ledipasvir (Harvoni®)[13] and ombitasvir/paritaprevir/ritonavir (Viekirax®)[35] and Technivie®),[34] have been approved for use in the United States, European Union, and/or in other regions.

In Japan, telaprevir (Telavic®) in combination with PegIFN/RBV, were the first approved DAAs for the treatment of chronic HCV infection in 2011. In November 2013, SMV (Sovriad®),[33] a protease inhibitor was approved for patients with genotype 1 and high HCV RNA levels, and in July 2014, the combination of asunaprevir (ASV) (Sunvepra®) and DCV (Daklinza) was approved for patients with genotype 1 This first IFN-free treatment combination allowed the treatment of IFN-ineligible patients and improved outcome in patients with prior nonresponse to IFN-based treatment. Since 2014, the fixed dose combinations SOF/LDV (Harvoni) and combination therapy with paritaprevir/ombitasvir/ritonavir (Viekirax) were approved for genotype 1. For IFN-free treatment of genotype 2, the combination of SOF (Sovaldi) with RBV was approved in March 2015.[2]

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 nonresponsiveness to PegIFN by increasing antiviral activity and reducing the risk of developing resistance-associated variants (RAVs). 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 antiHCV 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.[24]

The current open-label Phase 2a study is designed to investigate the safety, efficacy, and pharmacokinetics (PK) of an 8 or 12-week combination regimen of AL-335, ODV, and SMV in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection with or without compensated cirrhosis.

1.1.3. Background of AL-335

AL-335 is a uridine-based nucleoside monophosphate prodrug (or nucleotide analog) being developed in combination with ODV and SMV as an orally administered antiHCV 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.[16,17,18]

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 (EC_{50}) of 0.075 µM. The EC_{50} of AL-335 against chimeric replicons harboring the NS5B from genotypes 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 ^{14}C-AL-335 to rats and dogs, 15.0% and 36.0% of the administered radioactivity was recovered in urine. Oral administration of (nonlabeled) AL-335 revealed that AL-335 was recovered mainly as the metabolites in urine with only 0.0006% to 0.17% of AL-335 excreted in urine in rats and dogs. In contrast, 0.02% to 2.0% of ALS-022399 (metabolite) and 4.0% to 18.0% of ALS-022227 (metabolite) is excreted in urine in rats and dogs, respectively.

AL-335 (and its 2 metabolites ALS-022227 and ALS-022399; AL-335, the metabolites ALS-022399 and ALS-022227 are hereafter referred to as AL-335 [and metabolites]) are not expected to cause drug-drug interactions (DDIs) 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 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 (~10.0%) and body temperature (<1°C) were observed at the 1,000 mg/kg dose. All of these findings were monitorable and reversible, and all were considered nonadverse.

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, 40 healthy subjects had received single doses up to 1,200 mg (single ascending dose [SAD]) or multiple ascending doses (MADs) of AL-335 of 400 mg and 800 mg for 7 days (AL-335-601). This study also evaluated 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 to 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 to 45 minutes) and converted to ALS-022399. The terminal elimination half-life ($t_{1/2,term}$) of AL-335 was 30 to 60 minutes. In healthy subjects, 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 adverse events (SAEs), and no clinically relevant laboratory, electrocardiogram (ECG), Holter, vital sign, or physical examination safety signals have been identified. Three subjects reported 4 AEs, 1 of which emerged prior to dose administration. For the treatment-emergent AEs (TEAEs), 1 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 the study drug. The second TEAE, moderate dental pain (2 events), occurred 9 hours postdose and again 6 days after dosing. These events were assessed as unrelated to the study drug.

In the same Phase 1b study, multiple ascending doses of AL-335 (400 or 800 mg) over 7 days were evaluated in 20, 10, and 10 subjects with genotype 1, 2, or 3 chronic HCV infection, respectively. Thirty-two subjects received active study drug (400 or 800 mg AL-335 [genotype 1], or 800 mg only [genotypes 2 and 3]) and 8 received placebo. In Study AL-335-601, monotherapy with AL-335 800 mg once daily (qd) for 7 days resulted in a mean maximum decline in HCV RNA from baseline of 4.00 $\log_{10}$ IU/mL in HCV genotype 1 and of 4.46 $\log_{10}$ IU/mL and 4.72 $\log_{10}$ 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 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 2 subjects ≥10 days after the conclusion of dosing and were similar in magnitude to baseline (predose) levels. Three AEs occurred 1 time each: fatigue, common cold, and increased bilirubin. All AEs were mild (8 events) or moderate (8 events) in severity with the exception of 1 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 examination safety signals have been identified to date.

1.1.4. Background of ODV

ODV is an HCV NS5A inhibitor being developed in combination with AL-335 and SMV as an orally administered antiHCV therapeutic.

A summary of in vitro, nonclinical, and clinical data for ODV is provided below; more details can be found in the IB and its addendum.[19,20]

For details on the clinical studies including ODV, see Section 1.2.

In Vitro/Nonclinical Data

ODV is a highly potent HCV NS5A inhibitor with a mean EC_{50} of 5.3 pM and 26 pM against genotypes 1b and 1a HCV replicons, respectively, and 6.4 to 27 pM and 9.0 to 20 pM against chimeric replicons carrying NS5A from genotypes 1b and 1a clinical isolates, respectively. The EC_{50} values of ODV against chimeric replicons carrying the N-terminus of NS5A from representative strains of genotypes 2a, 2b, 3a, 4a, 5a, and 6a are 25, 215, 48, 8, 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 $t_{1/2,term}$ in plasma (rat: up to 55 hours; dog: up to 114 hours; monkey: 65.8 hours). The plasma half-life 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 97.0% or greater in rat, dog, and human plasma.

Preclinical data indicate that 91.0% to 98.0% of the administered oral dose of ODV is recovered in excreta by 168 hours postdose 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, OATP1B3, and is neither a substrate nor an inhibitor of transporters such as breast cancer resistance protein, multidrug resistance-associated protein (MRP)2, MRP3, and bile salt export pump. 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 dog cardiovascular studies, repeated dosing of ODV in dogs leading to exposure levels 14 times higher as compared to the target exposure in the current study was associated with ECG changes (prolonged PR and/or 1st degree atrioventricular [AV] block, prolonged QRS, QT, and corrected QT interval [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. 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, and 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 10.0% of C_{max} values by 4 to 5 days after dose administration. The 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 to 5 weeks. Plasma sampling beyond a 12-week Dose Period suggested that it would take approximately 20 to 24 weeks after the end of dosing to achieve effective clearance of the drug.

No clinically significant DDIs were observed between ODV and sovaprevir, 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 antiviral agents such as RBV, sovaprevir, 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 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 until treatment Week 12; this event evolved to a transient Type 1 2nd degree AV block. The cardiologist assessed the subject's 2nd 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 SMV

SMV is an HCV NS3/4A protease inhibitor approved in 2013 in the US, 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 other countries, and regions globally for the treatment of chronic HCV genotypes 1 and 4 infection with and without human immunodeficiency virus (HIV) coinfection. 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 postauthorization 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.[21,22] 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 EC_{50} and 90% effective concentration (EC_{90}) 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 EC_{50} values of 1.4 (N=78) and 0.4 (N=59) compared to reference genotype 1b replicon, respectively. Genotypes 1a and 1b isolates with a baseline Q80K polymorphism resulted in median FC in SMV EC_{50} 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 genotypes 4a, 4d, and 4 other 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 nonHCV-infected subjects were exposed to SMV and 8 studies conducted in Japan (4 Phase 3, 1 Phase 2 and 3 Phase 1 studies) including 434 HCV-infected treatment-naïve and treatment-experienced subjects who received SMV.

Pharmacokinetics

The blood to 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 61.0% after a high fat, high caloric breakfast (928 kcal) and by 69.0% 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, which 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 treatment-experienced subjects with chronic HCV genotype 1 with or without HIV-type 1 (HIV-1) coinfection and in subjects with chronic HCV genotype 4 infection, with no clinically relevant additional toxicity.[28,29]

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 TMC435350-TiDP16-C202, treatment-naïve subjects with HCV genotypes 2, 3, 4, 5, and 6 infections 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

genotypes 2, 4, 5, and 6. For the primary endpoint at Day 8, the mean (±standard error) 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 TMC435HPC3011 (RESTORE).

In Phase 2 Studies TMC435HPC2002 and TMC435HPC2014 (COSMOS and OSIRIS, respectively) and Phase 3 Studies TMC435HPC3017 (OPTIMIST-1), TMC435HPC3018 (OPTIMIST-2), and TMC435HPC3021 (PLUTO), high SVR at 12 weeks after the end-of-treatment (EOT) (SVR12) rates were observed in treatment-naïve and treatment-experienced HCV genotype 1- or genotype 4-infected subjects with and without cirrhosis treated with SMV and SOF; for more details on SMV in an all-oral combination regimen, refer to Section 1.2.

1.2. Background to All-oral DAA Combination Regimens

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

Combination of an NS3/4A Protease Inhibitor and a Nucleotide NS5B Polymerase Inhibitor: SMV/SOF

HCV genotype 1-infected subjects

In the Phase 2 Study TMC435HPC2002, 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 SVR12 rates (≥90.0%) 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 94.0%. Similar SVR12 rates were observed for HCV genotype 1a-infected subjects with and without baseline Q80K polymorphism.

In Phase 3 Studies TMC435HPC3017 and TMC435HPC3018, 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.

- The SVR12 rate of 96.8% in chronic HCV genotype 1-infected treatment-naïve or treatment-experienced subjects without cirrhosis treated with a 12-week SMV+SOF regimen was superior versus the historical control SVR12 rate of 87.0% (composite of approved DAA/PegIFN/RBV regimens). High SVR12 rates were observed for the 12-week regimen, regardless of the subgroup analyzed.
- The SVR12 rate of 82.6% in subjects treated with an 8-week SMV+SOF regimen in the TMC435HPC3017 study was not superior versus the historical control SVR12 rate of 83.0%. Higher SVR12 rates were observed among those subjects with more favorable demographic and baseline disease characteristics.

- The SVR12 rate of 83.5% in chronic HCV genotype-1 infected treatment-naïve or treatment-experienced subjects with cirrhosis treated with a 12-week SMV+SOF regimen in the TMC435HPC3018 study was superior versus the historical control SVR12 rate of 70%.

Pooled data from Studies TMC435HPC2002, TMC435HPC3017, and TMC435HPC3018, 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 adverse events 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 groups. 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 (AE of clinical interest) in subjects with cirrhosis.

HCV genotype 4-infected subjects

In the Phase 2a Study TMC435HPC2014, in HCV genotype 4-infected treatment-naïve and treatment-experienced (to prior IFN-based treatment with RBV) subjects who were treated with SMV 150 mg qd for 8 or 12 weeks in combination with SOF 400 mg qd, high SVR12 rates were observed. An SVR12 rate of 100% was observed after treatment for 12 weeks in subjects with and without cirrhosis and regardless of prior treatment history. An SVR12 rate of 75% was observed in subjects without cirrhosis who were treated for 8 weeks.

In Phase 3 Study TMC435HPC3021, HCV genotype 4-infected treatment-naïve and treatment-experienced (to prior IFN-based treatment with or without RBV) subjects were treated with SMV 150 mg qd for 12 weeks in combination with SOF 400 mg qd. Regardless of prior treatment history, 100.0% of subjects with and without cirrhosis achieved SVR12 and SVR 24 weeks after the EOT (SVR24).

Data from Studies TMC435HPC2014 and TMC435HPC3021 indicated that treatment of HCV genotype 4-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.

Combination of an NS3/4A Protease Inhibitor and an NS5A Inhibitor

SMV/DCV

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).[38] 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 10.0% (9/92) and 5.0% (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 the study drug). Serious adverse events occurred in 4.0% (4/92) and 9.0% (7/76) of subjects treated with SMV and DCV with and without RBV, respectively. Serious adverse events were related to study drug in 2 subjects (neurotoxicity, liver disorder). Adverse events leading to early discontinuation were reported in 2.0% (2/92) and 3.0% (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, and insomnia/sleep terror). Grade 3 or 4 hyperbilirubinemia occurred in 15.0% (14/92) and 4.0% (3/76) of subjects treated with SMV and DCV with and without RBV, respectively.

ODV/sovaprevir

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; sovaprevir 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 Groups 1 and 2, administration of sovaprevir, 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 2 weeks of study drugs. There have been 3 viral breakthroughs in Groups 1 and 2 each, and 1 viral relapse in Group 1, all occurring in subjects infected with the HCV genotype 1a. In contrast, no subjects with HCV genotype 1b infection have had viral breakthrough or relapse. Both combination dosing regimens were well tolerated with no drug-related SAEs and no discontinuations for safety. Trough concentrations of ODV were similar in Group 1 (200 mg sovaprevir) and Group 2 (400 mg sovaprevir), suggesting no effect of sovaprevir dose on ODV concentrations.

Combination of a Nucleotide NS5B Polymerase Inhibitor and a NS5A Inhibitor: ODV/SOF[1,15]

ACH102-017 was 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 (LFC) 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). Pharmacokinetic 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 $\log_{10}$ IU/mL (range: 5.5-7.8 $\log_{10}$ IU/mL). Group 2 included 6 subjects with HCV genotype 1a; median HCV RNA at baseline in Group 2 was 6.95 $\log_{10}$ IU/mL (range: 6.2-8.0 $\log_{10}$ IU/mL). All 12 (100.0%) subjects in Group 1 and all 12 (100.0%) subjects in Group 2 achieved SVR12 and subsequently 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 out of 6 subjects had interleukin-28B (IL28B) genotype nonCC (2 subjects with IL28B genotype TT) and median baseline HCV RNA was 6.32 $\log_{10}$ IU/mL (range: 6.0-7.3 $\log_{10}$ IU/mL). All 6 (100.0%) subjects achieved SVR12 and subsequently SVR24.

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

3-DAA Combination of an NS3/4A Protease Inhibitor, an NS5A Inhibitor, and a Nucleotide NS5B Polymerase Inhibitor: SMV/DCV/SOF, SMV/ODV/AL-335

At the time of the initial protocol writing, interim results from the Phase 2 IMPACT (TMC435HPC2010) 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 (100.0%) 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 ($AUC_{0\text{-}24h}$) by approximately 1.8-fold. SMV increased ODV exposure ($AUC_{0\text{-}24h}$) by 1.5-fold. Coadministration 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. All TEAEs (N=20) were assessed as mild (N=14) or moderate (N=6; oropharyngeal pain, tooth abscess, ALT increase, and fatigue

[3 events]), in severity by the investigator. The most commonly reported TEAEs (≥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 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±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 were available from an analysis with a cut-off date of 22 June 2016, which was 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 03 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 once every other day [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 subjects 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) had completed dosing. No cases of viral breakthrough or viral relapse were known to have occurred in any cohorts including 3-DAA treatment as of the 03 August 2016 data cut-off.

In Cohort 1b, HCV genotype-1a 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

visits 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 RAVs were observed at baseline in the 2 subjects with viral relapse, both infected with HCV genotype 1a. At the 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 and 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 had completed treatment and reached the follow-up Week 4 visit as of the 3 August 2016 cut-off, 1 subject infected with HCV genotype 1a was known to have experienced viral relapse. This viral relapse was identified on 02 August 2016 and viral sequencing was pending. No other cases of viral relapse or viral breakthrough were known to have occurred in any cohorts including 2-DAA treatment as of the 03 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 was generally safe and well tolerated. No clear safety signals have been identified in terms of TEAEs, 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 TEAEs had been reported. All TEAEs were mild (N=162 events) or moderate (N=11 events) in severity; no severe or life-threatening AEs were reported. The most commonly reported TEAEs (≥5% of the subjects) were 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 reeducated about dosing instructions and subsequently completed their treatment course. None of the reported TEAEs were 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 1 2nd degree 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 1 2nd degree AV block (SAE) described above. The second subject had an elevated PR interval (mean: 234 msec) at baseline, which did not change significantly postbaseline (maximum mean: 257 msec). This was not considered a TEAE;

however, in light of the 2nd 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 03 August 2016, no additional treatment-emergent SAEs, serious/life threatening TEAEs, or TEAEs 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 CK 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 postbaseline ECGs were considered to have an overall interpretation which was 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

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 analysis has not yet been conducted for AL-335.

Please see Section 1.1.3 and Section 1.2 for further details.

Known Benefits and Risks for ODV

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 to 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 treatment duration of 6 weeks has shown an efficacy of 100% SVR12 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 sovaprevir (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 infected with genotype 1a.

A formal adverse drug reaction analysis has not yet been conducted for ODV. However, an internal assessment of all preclinical and clinical information available at the time of the protocol writing has identified the effect of ODV on PR interval prolongation as a potential risk. Details are discussed in Section 1.3.2

Please see Section 1.1.4 and Section 1.2 for further details.

Known Benefits and Risks for SMV

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 genotypes 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 PegIFNα-2a/RBV or PegIFNα-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 a favorable safety/tolerability profile in Japanese and white HCV genotype 1 treatment-naïve and treatment-experienced subjects.

The Japan Phase 2/3 clinical data package included 1 Phase 2b and 4 Phase 3 studies (1 placebo-controlled and 3 open-label studies), including data for SMV 50 mg qd (TMC435-TiDP16-C215 only, N=40) and 100 mg qd (TMC435-TiDP16-C215: N=37, TMC435HPC3003: N=123, TMC435HPC3004: N=106, TMC435HPC3008: N=49, and TMC435HPC3010: N=79), all in combination with PegIFN/RBV. Data presented below focus on the SMV 100 mg data, the marketed SMV dose in Japan.

After administration of SMV 100 mg qd for 12 weeks in combination with PegIFNα-2a/RBV for 24 or 48 weeks in the Phase 3 studies conducted in Japan, including subjects with chronic HCV genotype 1 infection with a high viral load, SVR12 was achieved in 88.6% in treatment-naïve subjects (TMC435HPC3003), 95.9% in prior relapsers (TMC435HPC3008), and 52.8% in prior

nonresponders (TMC435HPC3004). For treatment-naïve subjects, the proportion of subjects achieving SVR12 was significantly higher in the SMV group compared to the placebo group (treatment with PegIFNα-2a/RBV alone) (61.7%). For both prior relapsers and prior nonresponders, the SVR12 rate in subjects who received SMV in combination with PegIFNα-2a/RBV was significantly higher than the SVR24 rates defined in the null hypothesis in subjects who received PegIFN/RBV (based on historical data). Similar efficacy data were obtained for SMV in combination with PegIFNα-2b/RBV.

Subgroup analyses based on age, baseline platelet count, and *IL28B* genotype showed high efficacy in all subgroups and no clear differences were noted across the subgroups.

PegIFN/RBV therapy could be shortened to 24 weeks in a high proportion of subjects based on response-guided therapy (RGT). In total, 91.9% of the SMV-treated treatment-naïve subjects (TMC435HPC3003) met the RGT criteria and completed the study treatment at Week 24, of whom 92.0% achieved SVR12. The majority of prior relapsers (TMC435HPC3008) and prior nonresponders (TMC435HPC3004) met the RGT criteria and could therefore, complete the study treatment at Week 24 (95.9% and 73.6%, respectively). The SVR12 rate was high (95.7%) in the prior relapsers and was 48.7% to 60.5% in prior nonresponders.

The TIGER study (TMC435HPC3005), 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 SMV 150 mg ($p\leq0.001$) 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 SMV 150 mg/PegIFN/RBV in Asian subjects from China and South Korea was similar to the known safety profile of SMV 150 mg in white 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 (>92.0%) 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 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 [70.0%]), it is recommended that HCV genotype 1-infected patients with cirrhosis are treated with SMV/SOF for 24 weeks.

SMV 150 mg qd in combination with SOF 400 mg qd for 8 weeks or 12 weeks in HCV genotype 4-infected subjects resulted in high SVR12 rates: an SVR12 rate of 100% was observed after treatment for 12 weeks in subjects with and without cirrhosis and regardless of prior

treatment history. An SVR12 rate of 75.0% was observed in subjects without cirrhosis who were treated for 8 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.

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 coinfection.

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 (TMC435-TiDP16-C208, TMC435-TiDP16-C216, and TMC435HPC3007 [PROMISE]) 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 placebo-treated subjects were pruritus (21.9% versus 14.6%), rash (21.8% versus 16.6%), blood bilirubin increased (7.4% versus 2.8%), photosensitivity reaction (4.7% versus 0.8%), and constipation (2.6% versus 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.

In the development of SMV in combination with PegIFN/RBV, the pooled analysis for the 5 Phase 2b/3 studies conducted in Japan (TMC435-TiDP16-C215, TMC435HPC3003, TMC435HPC3004, TMC435HPC3008, and TMC435HPC3010) indicated that SMV in combination with PegIFN/RBV was generally safe and well tolerated in subjects with chronic hepatitis C. In the pooled analysis, increased bilirubin-related events, which were defined as special interest for its potential as a signal for liver toxicity were observed in SMV 100 mg 12-week treatment group (31.5%, 104/330 subjects) and placebo group (8.2%, 6/73 subjects). However, the majority of the increased bilirubin-related events in SMV 100 mg 12-week treatment group were Grade 1 (18.5%, 61/330 subjects) or 2 (11.2%, 37/330 subjects) and transient and not associated with ALT or AST increases. The incidences of Grade 3 increased bilirubin-related events in SMV 100 mg 12-week treatment group were low (1.8%, 6/330), and no Grade 4 increased bilirubin-related events were reported. The incidences of Grade 3 rash events, serious events, and events that led to the discontinuation of all study drugs were low. The overall incidence of all rash-related events in the SMV group was lower than in the PegIFN/RBV group and the incidence of grade 3 rash related events and rash-related events leading to discontinuation of all study drugs were similar to those reported in the PegIFN/RBV group. Serious anemia-related events, grade 3 anemia-related events, and anemia related events leading

to discontinuation of all study drugs were reported only in the SMV group, but the incidences were low for all cases. The overall incidence of all anemia related events was similar to that reported in the PegIFN/RBV group. Additionally, the proportion of subjects who experienced temporary interruption or dose reduction of RBV due to anemia or hemoglobin decreased was similar between the treatment groups. No new clinically relevant safety concerns as compared to the global development program were identified.

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 TMC435HPC2002, TMC435HPC3017, and TMC435HPC3018 (SMV+SOF) studies. 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 coadministered 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).

Please see Section 1.1.5 and Section 1.2 for further details.

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 genotype or any other baseline factor, all without compromising patient compliance and safety.

1.3.2.2. Potential Risks

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 9.2.8.6).

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. Additional information about a potential QT effect in humans will be collected in a planned modified thorough QT study. ODV 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.

Preliminary data from an 8-week repeat-dose (70 mg/kg/day orally) mechanistic study in the telemetered dog 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. In this study, ODV was administered at a dose approximately 200 times higher than the dose planned for the current Study 64294178HPC2003. As information of exposure levels achieved with this dose is not available yet, a complete assessment of the clinical relevance of these findings is not yet possible. Importantly, analysis of all available echocardiography assessments from clinical studies in humans does not show any safety trends or signals (see below).

For more information refer to the Investigator's Brochure and its addendum.[19,20]

Summary of Cardiac Safety in Humans

A total of 440 subjects, of whom 75 were HCV-infected subjects and 365 were healthy subjects (ie, nonHCV 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 Fredericia (QTcF)[10] values over time were noted and there were no clinically significant findings identified in the echocardiograms.

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 subjects received AL-335+ODV±SMV. As of 22 June 2016, 97 subjects in Study AL-335-604 had enrolled and had received at least 1 dose of study drug (AL-335+ODV±SMV). The cardiac monitoring in these studies did not identify any clinically significant trends.

One SAE of asymptomatic 2nd 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 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 msec) at baseline which did not change significantly post baseline (maximum mean: 257 msec). This was not considered TEAE; 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.

In Study ACH102-005, a treatment-emergent PR prolongation was observed; this event evolved to a transient Type 1 2nd degree AV block. The cardiologist assessed the subject's 2nd degree AV block to be of undetermined etiology but unlikely due to study drug. The subject completed the full course of 12-week therapy with ODV and RBV. Based on the currently available data, the cardiac safety profile of ODV is acceptable to conduct the present study.

Continued surveillance for this potential risk will be done in this Phase 2 study via assessments of AEs and 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 9.2.8.7) and study wide treatment stopping rules (see Section 6.4) taking into account cardiac safety data of all ongoing studies including ODV dosing are included in the protocol. Finally 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).

Potential Risks for SMV

- **Hepatic Decompensation and Hepatic Failure**
  - Hepatic decompensation and hepatic failure, including fatal cases, have been reported postmarketing 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 6 months 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 coadministration of all 3 study drugs (SMV, ODV, and AL-335) resulted in a 7- to 9-fold, 2.5- to 2.7-fold, and 1- to 1.5-fold increase in AL-335, ALS-022399, and ALS-022227 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 were observed when the 3 study drugs were coadministered compared to SMV administered alone or ODV administered alone, respectively.
  - No clinically significant DDI was observed between ODV and sovaprevir, montelukast, atazanavir/ritonavir, efavirenz/emtricitabine/tenofovir disoproxil fumarate, darunavir/ritonavir, or raltegravir. ODV is a low-affinity substrate of OATP1B1 and an inhibitor of P-gp.
  - SMV is mainly metabolized by CYP3A enzymes. Coadministration of SMV and drugs that induce CYP3A enzymes may decrease SMV plasma concentrations and reduce its therapeutic effect. Conversely, coadministration 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**
  - The persistence of emergent AL-335-, ODV-, and/or SMV-RAVs could potentially impair a subject's future treatment options with respect to retreatment due to potential cross-resistance within the respective DAA class.
  - AL-335:

- In the MAD part of Study AL-335-601, 16 HCV genotype 1-, 8 HCV genotype 2-, and 8 HCV genotype 3-infected subjects received AL-335 (400 or 800 mg) for 7 days and 4 HCV genotype 1, 2 HCV genotype 2, and 2 HCV genotype 3 subjects received placebo for 7 days. Population sequencing of the HCV NS5B region was performed for 20 HCV genotype-1 infected 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 HCV genotype-1 infected subjects at any time point during the study. No other potential AL-335 RAVs were observed in these subjects.
- In the ongoing Study AL-335-604, 2 subjects (10%) in Cohort 1b, HCV genotype-1a infected subjects receiving the 2-DAA regimen of AL-335 and ODV (AL-335 800 mg qd+ODV 50 mg qod without SMV for 8 weeks) experienced viral relapse. At the 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 and Y93H in combination with T21A in the other subject) and no emerging AL-335 RAVs. Further, 1 HCV genotype-1a infected subject in Cohort 4, receiving AL-335 800 mg qd+ODV 50 mg qod without SMV for 8 weeks experienced viral relapse. Viral sequencing data of this subject at the time of viral relapse was pending.

– ODV:

- 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 preexisting mutations associated with NS5A inhibitor resistance. In 2 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 2 subjects, multiple NS5A amino acid substitutions (3 up to 6) were detected at baseline. Three out of 6 subjects who achieved HCV RNA levels less than the LLOQ 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 sovaprevir 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.
- In the ongoing Study AL-335-604, 2 subjects (10%) in Cohort 1b, HCV genotype-1a infected subjects receiving the 2-DAA regimen of AL-335 and ODV (AL-335 800 mg qd+ODV 50 mg qod without SMV for 8 weeks) experienced viral relapse. At the 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 and Y93H in combination with T21A in the other subject) and no emerging AL-335 RAVs. Further, 1 HCV genotype-1a infected subject in Cohort 4, receiving AL-335 800 mg qd+ODV 50 mg qod without SMV for 8 weeks experienced viral relapse. Viral sequencing data of this subject at the time of viral relapse was pending.

- SMV:
  - 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 TMC435-TiDP16-C205, TMC435-TiDP16-C206, TMC435-TiDP16-C208, TMC435-TiDP16-C216, and TMC435HPC3007, emerging mutations at NS3 positions 80, 122, 155 and/or 168 were observed in 180 of 197 (91.0%) 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 Phase 3 studies showed that emerging RAVs were no longer detectable by standard population sequencing in 90 of 180 (50.0%) subjects within the study period (median follow-up time 28 weeks; range: 0 to 70 weeks).
  - In the TMC435HPC3011 study in HCV genotype 4-infected subjects, 28 of 32 (88.0%) 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 of 32 [75.0%] subjects), similar to the emerging mutations observed in HCV genotype 1-infected subjects.
  - In the TIGER study, 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 (10 of 13 [76.9%] 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 of the 6 subjects in Study TMC435HPC2002, 1 of the 3 subjects in Study TMC435HPC3017, and 11 of the 13 subjects in Study TMC435HPC3018. 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 TMC435HPC3017 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 the available nonclinical and clinical data, cardiac monitoring is conducted through ECGs and regular echocardiograms (see the TIME AND EVENTS SCHEDULE). In addition, a toxicity management plan for cardiac events is included in the protocol (see Section 9.2.8.7) 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, ECGs, 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 the subject's last study visit.

- DRC will be established to monitor data with focus on the safety and on the general conduct of the study. The DRC is a committee within the sponsor's organization that is independent of the sponsor's study team.
- 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 9.2.8), 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).

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 rates 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 study is designed to investigate the safety, efficacy, and PK of administration of an 8 or 12-week regimen 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, in Japanese subjects with chronic hepatitis C genotype 1 or 2 virus infection with or without compensated cirrhosis who are DAA treatment-naïve (DAA-naïve, defined as not having received treatment with any approved or investigational DAA for chronic HCV infection; prior HCV therapy consisting of IFN [pegylated or nonpegylated] with or without RBV is allowed). 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. In Japan, SMV is not approved for patients with cirrhosis; therefore, subjects with compensated cirrhosis will be enrolled in a separate cohort and will be monitored closely for safety and tolerability.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objectives

- To evaluate the safety and tolerability of a combination treatment of AL-335, ODV, and SMV for 8 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection without cirrhosis and for 12 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection with compensated cirrhosis.

Secondary Objectives

- To evaluate the PK of AL-335 (and metabolites), ODV, and SMV in plasma in Japanese subjects with genotype 1 or 2 chronic HCV infection with or without compensated cirrhosis who are DAA-naïve.
- To evaluate the efficacy, ie, SVR4, SVR12, and SVR24, of a combination treatment with AL-335, ODV, and SMV for 8 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection without cirrhosis and for 12 weeks in DAA-naïve Japanese subjects with genotype 1 or 2 chronic HCV infection with compensated cirrhosis.
- To evaluate on-treatment viral kinetics in an 8 or 12-week treatment regimen containing AL-335, ODV, and SMV in subjects who are DAA- naïve.
- To evaluate the incidence of on-treatment failure during an 8 or 12-week treatment regimen containing AL-335, ODV, and SMV in subjects who are DAA-naïve.
- To evaluate the incidence of viral relapse after an 8 or 12-week treatment regimen containing AL-335, ODV, and SMV in subjects who are DAA-naïve.

Exploratory Objectives

- To explore relationships of exposure of AL-335 (and metabolites), ODV, and SMV with SVR and safety.
- To evaluate the impact of the patient and disease characteristics at baseline on SVR, including but not limited to prior treatment history, *IL28B* genotype, presence of cirrhosis, HCV RNA level, and HCV geno/subtype.
- To evaluate the impact of the presence of HCV NS3/4A, NS5A, and/or NS5B polymorphisms at baseline on treatment outcome.
- To assess the emergence of resistant variants in subjects not achieving SVR.

2.1.2. Endpoints

Primary Endpoint

- Safety data, including but not limited to AEs, physical examination, vital signs, 12-lead ECGs, echocardiograms, and clinical laboratory results (including chemistry, hematology, and urine)

Secondary Endpoints

- PK parameters for AL-335 (and metabolites), ODV, and SMV in plasma
- The proportion of subjects who have an SVR4, SVR12, and SVR24
- The proportion of subjects with viral relapse
- The proportion of subjects with on-treatment failure
- The proportion of subjects with on-treatment virologic response:
  - HCV RNA not detected
  - HCV RNA <LLOQ
- Time to achieve HCV RNA not detected or HCV RNA <LLOQ

Exploratory Endpoints

- The effect of the presence or absence at baseline of HCV NS5A, NS5B, and/or NS3/4A polymorphisms on treatment outcome
- The changes in the HCV NS3/4A, NS5A and/or NS5B sequences in subjects not achieving SVR
- Impact of baseline condition on SVR (including but not limited to prior treatment history, *IL28B* genotype, presence of cirrhosis, HCV RNA level, and HCV geno/subtype)

Refer to Section 9, Study Evaluations for evaluations related to endpoints.

2.2. Hypothesis

The study is hypothesis-generating. No formal hypothesis will be tested.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a Phase 2a, multicenter, open-label study to investigate the safety, efficacy, and PK of an 8 or 12-week treatment regimen with AL-335, ODV, and SMV in Japanese subjects with genotype 1 or 2 chronic HCV infection with or without compensated cirrhosis who are DAA-naïve, followed by a 24-week posttreatment follow-up.

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 Period can be extended if discussed with and approved (documented) by the sponsor. Thereafter, if eligible, subjects will be assigned to 1 of the 2 treatment cohorts to receive AL-335, ODV, and SMV combination treatment for 8 or 12 weeks based on the absence or presence of compensated cirrhosis. A posttreatment follow-up until 24 weeks after the actual EOT is included to assess SVR4, SVR12, and SVR24. The total study duration for each subject will be approximately 38 or 42 weeks (including the 6-week Screening Period, the 8 or 12-week Treatment Period, and the 24-week Posttreatment Follow-up Period). The study will be considered to be completed with the last visit of the last subject participating in the study.

Approximately 20 DAA-naïve chronic HCV genotype 1 or 2-infected subjects without cirrhosis will be assigned to Cohort 1, and approximately 20 DAA-naïve HCV genotype 1 or 2-infected subjects with compensated cirrhosis will be assigned to Cohort 2.

- Cohort 1 (N=20, chronic hepatitis C without cirrhosis): AL-335 800 mg qd+ODV 25 mg qd+SMV 75 mg qd for 8 weeks
- Cohort 2 (N=20, chronic hepatitis C with compensated cirrhosis): AL-335 800 mg qd+ODV 25 mg qd+SMV 75 mg qd for 12 weeks

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).

If study drug 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 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 Visit need to be performed.

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 increase of >1.0 $\log_{10}$ IU/mL in HCV RNA from nadir or confirmed HCV RNA >2.0 $\log_{10}$ IU/mL in subjects who had previously achieved HCV RNA <LLOQ (detected or not detected) while on treatment.

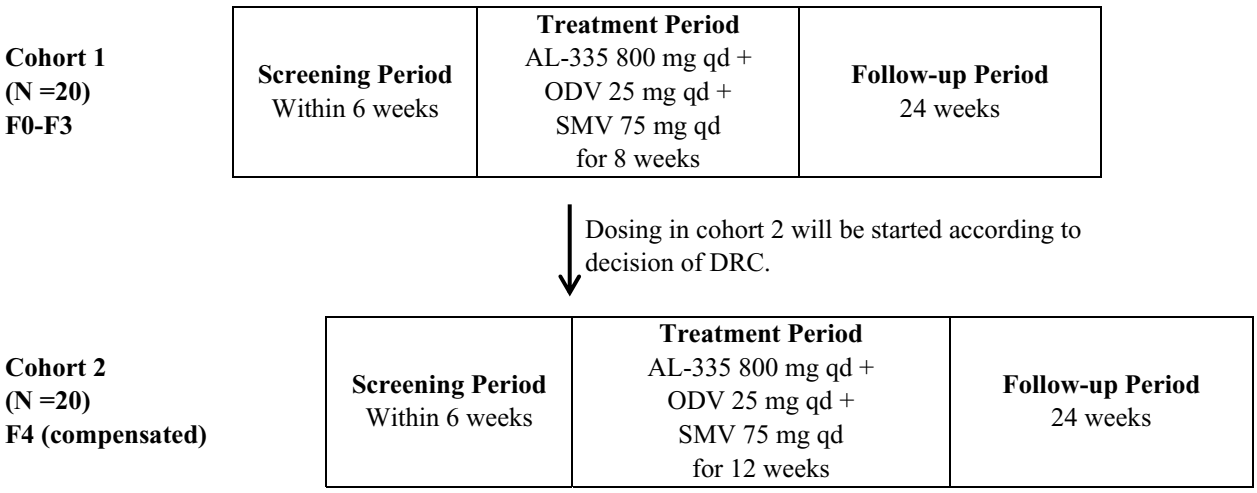
A DRC will be established to monitor data with focus on the safety and on the general conduct of the study. The DRC is a committee within the sponsor's organization that is independent of the sponsor's study team. Details will be specified in a separate charter.

The primary objective of this study is to assess safety and tolerability of the 3 DAA combination in Japanese patients with and without compensated liver cirrhosis. Compared to subjects with chronic hepatitis C without cirrhosis (enrolled in cohort 1), subjects with chronic hepatitis C with compensated cirrhosis (enrolled in cohort 2) are considered to potentially have a higher safety risk. To conduct this study carefully in light of securing subjects' safety, dosing of cohort 2 with patients with compensated cirrhosis will only start after a DRC has reviewed all available relevant safety data when the first 6 subjects in cohort 1 completed the Week 4 visit (including but not limited to AE, SAE, clinical laboratory test) and no new or unexpected events, which are considered clinically significant, are detected. DRC may require to review data of further patients before deciding about the start of dosing in cohort 2. Enrollment in cohort 1 will be kept ongoing during the data review process.

All study drugs (AL-335, ODV, and SMV) should be taken together in the morning at approximately the same time with food (ie, during or within 15 minutes after completion of a meal). Intake of study drugs should take place on site during visits when biochemistry samples are to be taken after fasting for at least 8 hours, and when predose PK sampling (sparse and rich sampling) is performed. For more information on the dose selection, see Section 3.2.

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



Key: ODV=odalasvir; qd=once daily; SMV=simeprevir

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.

Efficacy of the regimen will be assessed by means of HCV RNA levels at all scheduled visits (see Section 9.5.1). HCV RNA levels will be processed in real time, and results will be communicated to the sponsor and the investigator throughout the study. For resistance determination, blood samples will be collected throughout the study (see Section 9.5.2).

Blood samples will be collected to assess the PK in the rich serial PK substudy at Week 4 Visit, at 10 different time points within the dosing interval, for the measurement of plasma concentrations of AL-335 (and metabolites), ODV, and SMV, in approximately more than 12 subjects (approximately more than 6 subjects from Cohort 1 and Cohort 2, each). Sparse PK sampling for AL-335 (and metabolites), ODV, and SMV will be performed in all subjects including subjects participating in the rich serial PK substudy. Sparse PK sample will be taken at predose, between 2-to 4-hours postdose, and between 4-to 6-hours postdose at Weeks 2, 4, 6, and at the EOT (Week 8) Visit (Cohort 1), or Weeks 2, 4, 6, 8 and at the EOT (Week 12) Visit (Cohort 2). At Week 4, no sparse PK sample will be taken for subjects participating in the rich

serial PK substudy. At the Week 12 Follow-up Visit, sparse PK sample will be taken at any time for the measurement of plasma concentrations of ODV. Intake of study drugs should take place on site when predose PK sampling (sparse and rich sampling) is performed. At the EOT Visit, intake of study drugs should take place on site when predose PK sampling (sparse and rich sampling) is performed. (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) (see Section 9.6).

The safety evaluations will include monitoring of AEs, clinical laboratory tests, ECGs, echocardiograms, vital sign measurements, and physical examinations. Specific toxicity management plans in line with the known pharmacologic profile of the study drugs (and the drug class) evaluated in this study will be implemented (see Section 9.2).

Subjects will complete all above mentioned assessments during study-related visits as specified in the TIME AND EVENTS SCHEDULE.

3.2. Study Design Rationale

Dose and Treatment Duration

The present study will evaluate a 3-DAA regimen of AL-335 800 mg qd, ODV 25 mg qd, and SMV 75 mg qd, coadministered with food (as individual tablets/capsules) for 8 weeks in DAA-naïve Japanese subjects without cirrhosis or 12 weeks in DAA-naïve Japanese subjects with compensated cirrhosis.

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 antiHCV 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.

The study population will include chronic HCV genotype 1 or 2-infected Japanese subjects who are DAA-naïve.

Selection of Doses for AL-335, ODV, and SMV

AL-335 dose selection

Pharmacokinetic 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 the 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 being evaluated in 20 treatment-naïve subjects with chronic HCV infection without cirrhosis. 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 prodrug 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 in HCV genotype 1-infected subjects, showed 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 $\log_{10}$ IU/mL for the 800 mg dose compared to 2.76 $\log_{10}$ IU/mL for the 400 mg dose). In addition, 7 days of monotherapy with AL-335 at 800 mg qd in HCV genotypes 2- and 3-infected subjects showed potent suppression of viral replication with a mean maximum decrease in HCV RNA from baseline of 4.46 $\log_{10}$ IU/mL and 4.72 $\log_{10}$ IU/mL for genotypes 2 and 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 2a 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). No treatment-related SAEs, and no clinically relevant laboratory, ECG, Holter, vital signs, or physical examination safety signals were identified when AL-335 was administered as monotherapy. Preliminary safety evaluation of the first 80 subjects who were dosed for 6 or 8 weeks with AL-335 and ODV with or without SMV in the ongoing Phase 2a Study AL-335-604, revealed no safety signals in AEs, laboratory tests, ECGs, echocardiograms, vital signs, or physical examinations. One cardiac-related SAE was reported in a subject with progressive prolongation of PR interval and development of Type 1 2nd degree 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 subjects, potent antiviral activity was demonstrated for all doses.

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 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 25 mg/day (50 mg every other day) in the cohorts of Phase 2a Study AL-335-604, and in the current Phase 2a study.

SMV dose selection

Although SMV exposure was increased by 1.6-fold when administered in combination with ODV compared to SMV administered alone in the DDI study, AL-335-602 in healthy volunteers, results from the Phase 2a Study AL-335-604, indicated that there is no significant interaction when these compounds are administered to HCV subjects. In the 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 together 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 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 a dose of 75 mg.

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

Selection of treatment duration

In the current study, an 8 and 12-week treatment course of AL-335, ODV, and SMV will be investigated in treatment-naïve Japanese subjects with chronic HCV genotype 1 or 2 infection with or without compensated cirrhosis.

In subjects with chronic HCV infection and compensated liver disease, 12-week treatment with 2 DAAs has been demonstrated to lead to high SVR rates (see also Section 1.2, Background to All-oral IFN-free DAA Combination Regimens). Combination regimens consisting of 3 DAAs have been shown to increase the speed with which HCV RNA declines to undetectable levels,[23] suggesting a more robust inhibition of HCV replication.

It is anticipated that combinations of 3 DAAs with different mechanisms of action will provide a higher antiviral pressure on HCV in patients with decompensated liver disease leading to higher SVR rates compared to less robust regimens.

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 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 the ongoing Study AL-335-604, to date, no cases of viral failure or relapse have been observed in 3-DAA arms, whereas, 3 cases of viral relapse were observed in Cohorts 1b and 4 in which AL-335 and ODV were dosed without SMV; therefore, it is anticipated that addition of a third DAA will yield in higher SVR rates. 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 qod, and SMV 75 mg qd for 8 or 6 weeks, respectively, all subjects achieved SVR12 and SVR4, respectively.

In patients with compensated cirrhosis, based on preliminary data from Phase 2 study AL-335-604, suggesting further benefit, treatment durations of 8 and 12 weeks are studied in additional cohorts (Phase 2b). The outcome of this study will inform the duration evaluated in Phase 3 for patients with compensated cirrhosis. To assess safety, PK and efficacy of the potentially longest treatment duration in Japanese subjects with compensated cirrhosis before going to Phase 3, the Sponsor decided to extend the treatment duration of the cirrhotic cohort 2 in this study from 8 to 12 weeks.

Pharmacogenomic (DNA) Evaluations

A genetic polymorphism upstream of the *IL28B* gene (single nucleotide polymorphism rs12979860) has been associated with viral clearance in response to PegIFN/RBV treatment.[11] Analyses of pooled data from 2 Phase 3 studies, in which SMV and PegIFN/RBV were combined, also showed lower SVR12 rates in subjects with *IL28B* genotype TT versus CT and CC. The role of this polymorphism in novel treatment regimens for HCV consisting of DAAs without PegIFN/RBV has not been established. The present study will assess the influence of this polymorphic genetic marker on the treatment response to the drug regimen investigated in this study (see Section 9.6, Pharmacogenomic Evaluations).

Study Population

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

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 Sections 1.1.4 and 1.1.3, respectively), is expected to provide in combination with SMV, an effective treatment for HCV genotypes 1 to 6-infected patients.

In Japan, approximately 70% of HCV-infected patients have genotype 1 infection and approximately 30% have genotype 2 infection. Based on this epidemiology data, this study will include treatment-naïve Japanese subjects with HCV genotype 1 or 2 infection. Subjects will be assigned to 2 separate cohorts (Cohort 1 or Cohort 2) based on the absence or presence of compensated cirrhosis. This study aims to include 40 subjects (20 subjects per cohort).

4. SUBJECT POPULATION

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 must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

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

1. Man or woman, 20 to 75 years of age, inclusive.

2. Body mass index; weight in kg divided by the square of height in meters) of 18.0 to 35.0 kg/m^2, 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. All subjects must have HCV genotype 1 or 2 infection, determined at screening.

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

5. HCV RNA plasma levels ≥10,000 IU/mL, determined at screening.

6. DAA-naïve subjects, defined as not having received treatment with any approved or investigational DAA drug for chronic HCV infection; prior HCV therapy consisting of IFN (pegylated or nonpegylated) with or without RBV is allowed.

7. Subjects with chronic Hepatitis C without 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)

Subjects with chronic Hepatitis C with compensated cirrhosis (not meeting the criterion for hepatic decompensation described in the Exclusion Criteria #6 [Section 4.2]), defined as any of the following:

- Fibroscan (prior report or during Screening Period) with a result of >12.5 kPA, OR
- Liver biopsy (prior report or during Screening Period) showing cirrhosis (eg, METAVIR score of F4 or Ishak score ≥5).

8. A woman of childbearing potential must have a negative highly sensitive serum pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening.

9. 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.

Before enrollment, a woman must be either:

a. not of childbearing potential defined as:
   - o postmenopausal (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
   - o be surgically sterile (have had a total hysterectomy, bilateral oophorectomy, or bilateral tubal ligation/bilateral tubal clips without reversal operation), or otherwise be incapable of pregnancy

OR

b. of childbearing potential and

– not heterosexually active (eg, abstinence) from at least 14 days prior to Day 1 until 12 weeks after the EOT (or longer, if dictated by local regulations), OR
   - o have a vasectomized partner (confirmed sterile per verbal account of the subject), OR
   - o if heterosexually active, be practicing an acceptable method of birth control from at least 14 days prior to 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. Oral hormone-based contraceptives are not allowed from 14 days before baseline until the Week 4 Follow-up Visit. An intrauterine device, being either hormonal (ie, intrauterine hormone-releasing system (IUS)* or nonhormonal, is considered highly effective and reliable, therefore, subjects are not required to use additional contraceptive methods (no double-barrier method

required). Other nonoral 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.

**Non-oral hormone based contraception methods (eg, injectable, implants, transdermal system, vaginal ring), cervical cap and diaphragm with spermicide are not approved in Japan.

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. Women 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.

11. Women must have a negative highly sensitive urine pregnancy test at Day 1.

12. 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.

Before enrollment, a man must either:

a. be surgically sterile (had a vasectomy), or otherwise incapable of fathering a child

OR

b. not be heterosexually active (eg, abstinence) from at least 14 days prior to Day 1 until at least 12 weeks after the EOT, OR

c. if heterosexually active, have a partner who is postmenopausal (2 years amenorrhea), surgically sterile (has had a total hysterectomy, bilateral oophorectomy, or bilateral tubal ligation/bilateral tubal clips without reversal operation), or otherwise incapable of becoming pregnant, OR

d. if heterosexually active with a woman of childbearing potential, be

practicing an acceptable method of birth control from at least 14 days prior to 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 men is a double-barrier method (eg, male condom+either diaphragm or cervical cap with or without spermicide)*. Men with a female partner who uses hormonal contraceptives (oral, injectable, or implants)*, a hormonal (IUS), or nonhormonal intrauterine device, and men who are vasectomized or otherwise incapable of fathering a child are not required to use additional contraceptive methods.

*Non-oral hormone based contraception methods (eg, injectable, implants, transdermal system, vaginal ring), cervical cap and diaphragm with spermicide are not approved in Japan.

See Notes 1 and 2 of the inclusion criteria #9.

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

14. Willing and able to adhere to the prohibitions and restrictions specified in this protocol (Section 4.3).

15. 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.

16. Must voluntarily sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

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 (HIV-1 or HIV-2 antibody positive) or hepatitis B virus (HBV) (hepatitis B surface antigen [HBsAg] positive).

3. Infection with HCV genotype 3, 4, 5, or 6.

4. Prior treatment with any investigational or approved HCV DAA, either in combination with PegIFN or IFN-free.

5. Any evidence of liver disease of nonHCV etiology. This includes, but is not limited to, acute hepatitis A infection (immunoglobulin M), drug- or alcohol-related liver disease, autoimmune hepatitis, hemochromatosis, Wilson's disease, alpha-1 antitrypsin

deficiency, primary biliary cirrhosis, or any other nonHCV liver disease that is considered clinically significant by the investigator.

6. Evidence of hepatic decompensation as assessed with Child-Pugh Class B or C or any of the following: 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, which is considered cured with minimal risk of recurrence) and history of hepatocellular carcinoma regardless of period before screening.

9. Known allergies, hypersensitivity, or intolerance to AL-335, ODV, or SMV, or their excipients (refer to IBs and addenda of AL-335,[18,16] ODV, [19,20] and SMV.[21,22]

10. Presence of significant comorbidities, 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, 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) <55.0% or any other echocardiogram finding suggestive of clinically relevant cardiomyopathy
    - screening abnormal ECG findings such as: significantly abnormal PR [PR interval >200 msec], QRS intervals or QTc >450 msec for male subjects and >470 msec for female subjects (based on the average of the 3 ECGs)
    - evidence of any heart block
    - evidence of right bundle branch block or left bundle branch block
    - history or family history of prolonged QT syndrome (eg, torsade de pointes) or sudden cardiac death

13. Any of the following laboratory abnormalities at screening:

    - platelet count $<75\times10^3/\mu L$ or $<75\times10^9/L$
    - hemoglobin <11 g/dL or <6.83 mmol/L for male subjects, <10 g/dL or

<6.21 mmol/L for female subjects

- absolute neutrophil count <$1.00\times10^3/\mu L$
- ALT and/or AST >10× upper limit of normal (ULN)
- total serum bilirubin >1.5×ULN
- albumin <3.5 g/dL or <35 g/L
- estimated glomerular filtration rate (eGFR) of <50 mL/min/1.73m^2
- hypo-/hyperkalemia (Grade 2 or higher)

14. 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.

15. Subject is pregnant, planning to become pregnant (during treatment and up to 12 weeks after the EOT), or breast-feeding female subject (including female subject who discontinues breast-feeding), or male subject whose female partner is pregnant or planning to become pregnant (during treatment and up to 12 weeks after the EOT).

16. 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.

17. Have findings suggestive of hepatocellular carcinoma. Subjects with cirrhosis have to receive an ultrasound scan, computed tomography (CT) scan, or magnetic resonance imaging (MRI) within 3 months prior to baseline/Day 1 to document the absence of findings suggestive of hepatocellular carcinoma.

NOTE: Retesting of laboratory values (eg, safety laboratory or HCV RNA) that lead to exclusion will be allowed once during the Screening Period to assess eligibility.

Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available 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 during the course of the study to be eligible for participation:

1. Refer to Section 8, PRESTUDY AND CONCOMITANT THERAPY for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements) (Sections 4.1 and 4.2).

3. 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. Subjects should be advised to use sun protective measures (such as a hat, sunglasses, protective clothing, sunscreen) during treatment with SMV.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Randomization will not be used in this study. Subjects will be assigned to a treatment cohort based on the presence or absence of cirrhosis.

Blinding

As this is an open-label 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-335 800 mg qd, ODV 25 mg qd, and SMV 75 mg qd. The treatment duration is 8 weeks for subjects without cirrhosis and 12 weeks for subjects with compensated cirrhosis.

All study drugs should be taken together in the morning at approximately the same time with food (ie, during or within 15 minutes after completion of a meal).

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 subjects without cirrhosis or on Day 1, Week 4

and 8 for subjects with compensated cirrhosis. Subjects will be instructed to continue intake of study drugs up to 8 or 12 weeks of treatment, 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.

AL-335 (800 mg), ODV (25 mg), and SMV (75 mg) will be dosed qd in a fed state starting on Day 1, after the baseline assessments have been completed.

All study drugs should be taken together in the morning at approximately the same time with food (ie, during or within 15 minutes after completion of a meal). Intake of study drugs should take place on site during visits when biochemistry samples are to be taken after fasting for at least 8 hours, and when predose PK sampling (sparse and rich sampling) is performed. (see the TIME AND EVENTS SCHEDULE and TIME AND EVENTS SCHEDULE: Rich serial PK Assessments). 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 treatment discontinuation is withdrawal of consent. Additional unscheduled visits may be performed for safety or tolerability reasons, if needed. Subjects who withdraw consent during the Treatment or Posttreatment Follow-up Period will be offered an optional safety Follow-up Visit which needs to be scheduled 4 weeks after EOT.

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

6.3. Treatment Stopping Rules (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 >2.0 $\log_{10}$ IU/mL in subjects who had previously achieved HCV RNA <LLOQ (detected or not detected) while on treatment. 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 the study drug is necessary, a 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.

For details on the assessments during the Treatment Withdrawal Visit, see the TIME AND EVENTS SCHEDULE.

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 recruitment and dosing in all subjects in this study if the event(s) is adjudicated by the DRC to be at least possibly related to the study regimen. Such event(s) will be reported to the sponsor medical monitor within 24 hours. Upon this notification, a safety assessment of the event by the DRC will take place within 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.

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 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) in the diary. On the days of PK assessments which are part of the rich PK substudy, the start and end times of the accompanying meal should be documented; on the previous day and on the day after PK samples (after 24h PK sample collected) which are part of the rich 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) in the diary. 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. A study-site personnel is to review the medication diary for adherence and perform adherence counseling at each on-treatment study visit. 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) and phlebotomy is disallowed from baseline until EOT and from screening until the Week 12 Follow-up Visit, respectively.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; nonpharmacologic therapies such as electrical stimulation, acupuncture, special diets, or exercise regimens) used during the study and different from the study drugs (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 4.1.

AL-335 is metabolized by esterases and is not a substrate of any CYP enzymes. AL-335 (and metabolites) 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. Coadministration 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 OATP1B1, OATP1B3, breast cancer resistance protein, MRP2, MRP3, and bile salt export pump. 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. Coadministration 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. Coadministration 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. Coadministration of SMV with inhibitors of CYP3A may increase SMV plasma concentrations. Clinically, SMV inhibits uptake transporters OATP1B1, OATP1B3, and the efflux transporters P-gp/MRP1 and MRP2. Coadministration of SMV with drugs that are substrates for OATP1B1, OATP1B3, and P-gp transport may result in increased plasma concentrations of such drugs.

An overview of disallowed concomitant medications is presented in Table 1.

Table 1: Disallowed Medications

Disallowed within 30 days of screening until the end of follow up
● All nonHCV investigational drugs or invasive investigational medical devices ● Experimental nonHCV vaccines Note*: Approved nonHCV vaccines are allowed.*
Disallowed within 3 months prior to screening until the end of the study
● Antiarrhythmic: amiodarone
Disallowed from screening until the end of the study
● All concomitant medications with a potential to prolong QT interval (eg, digoxin)

- 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:
  - Amantadine, Amitriptyline, Amphotericin B, Anagrelide, Apomorphine, Aripiprazole, Arsenic trioxide, Asenapine, Atazanavir, Atomoxetine, Azithromycin, Bepridil, Bortezomib, Bosutinib, Buprenorphine, Capecitabine, Ceritinib, Chloral hydrate, Chloroquine, Chlorpromazine, Cilostazol, Ciprofloxacin, Citalopram, Clarithromycin, Clomipramine, Clozapine, Cocaine, Crizotinib, Dabrafenib, Dasatinib, Degarelix, Delamanid, Dexmedetomidine, Diphenhydramine, Disopyramide, Domperidone, Donepezil, Droperidol, Efavirenz, Eribulin mesylate, Erythromycin, Escitalopram, Esomeprazole, Famotidine, Fingolimod, Flecainide, Fluconazole, Fluvoxamine, Foscarnet, Furosemide, Galantamine, Garenoxacin, Gatifloxacin, Granisetron, Haloperidol, Hydrochlorothiazide, Hydroxychloroquine, Hydroxyzine, Imipramine, Indapamide, Itraconazole, Ketoconazole, Lansoprazole, Lapatinib, Lenvatinib, Leuprolide, Levofloxacin, Levomepromazine, Lithium, Loperamide, Methadone, Metoclopramide, Metronidazole, Mirabegron, Mirtazapine, Moxifloxacin, Nelfinavir, Nicardipine, Nilotinib, Norfloxacin, Nortriptyline, Ofloxacin, Olanzapine, Omeprazole, Ondansetron, Osimertinib, Oxaliplatin, Oxytocin, Paliperidone, Panobinostat, Papaverine HCl, Paroxetine, Pasireotide, Pazopanib, Pentamidine, Perphenazine, Pimozide, Pipamperone, Probucol, Procainamide, Promethazine, Propofol, Quetiapine, Quinidine, Quinine, Rilpivirine, Risperidone, Ritonavir, Roxithromycin, Saquinavir, Sertraline, Sevoflurane, Solifenacin, Sorafenib, Sotalol, Sulpiride, Sultopride, Sunitinib, Tacrolimus, Tamoxifen, Telaprevir, Tetrabenazine, Tiapride, Tizanidine, Tolterodine, Toremifene, Torsemide, Trazodone, Trimipramine, Vandetanib, Vardenafil, Vemurafenib, Venlafaxine, Voriconazole, Vorinostat, Zotepin

Note*: Please refer the comprehensive list of drugs, which include approved drugs overseas, 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.* [5]

Disallowed from screening until the Week 12 Follow-up Visit

- Prescription drugs for improvement of hepatic function which could potentially affect to hepatic function including AST and ALT (eg. glycyrrhizinate, ursodeocycholic Acid)

Disallowed from screening onwards until the end-of-treatment

- Immunomodulators (eg, cyclosporine, interleukins, or systemic corticosteroids in immunosuppressive dose)
- Any herbal or nutritional products for HCV treatment including silibinin, silybin, and silymarin (milk thistle)
- Antiarrhythmics: mexiletine, systemic lidocaine, and propafenone
- Beta-blockers
- Proton-pump inhibitors (eg, rabeprazole)
- Ca-channel blockers (eg, amlodipine, bepridil, diltiazem, felodipine, nifedipine, nisoldipine,verapamil)
- Na-channel blockers (eg, lidocaine, mexiletine, moricizine, propafenone, tocainide)
- K-channel blockers (eg, bretylium, dronedarone, ibutilide, dofetilide)

Disallowed from 2 weeks before baseline and during the Treatment Period

- Potent and moderate CYP3A4 inducers, such as:
  - Antiepileptics: carbamazepine, oxcarbazepine, (fos)phenytoin, phenobarbital
  - Antituberculosis drugs: rifabutin, rifampicin, and rifapentine
  - Systemic dexamethasone (if more than a single dose)
  - Miscellaneous: products containing *Hypericum perforatum* (St. John's Wort)
- P-gp inhibitors

Disallowed from baseline onwards until the end-of-treatment

- Potent and moderate CYP3A4 inhibitors, such as:
  - Antibiotics (systemic): troleandomycin, and telithromycin
  - Antiretrovirals: (fos)amprenavir, delavirdine, darunavir, etravirine, indinavir, lopinavir, nevirapine, 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 the Week 4 Follow-up Visit

- Oral contraceptives

Key: CYP=cytochrome P450; HCV=hepatitis C virus; P-gp=P-glycoprotein
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 Week 4 Follow-up Visit.

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 adverse events and desired efficacy.
● Analgesics: ergoloid mesylates, ergotamine tartrate, dihydroergotamine, and methylergonovine
● Lipid-lowering drugs: atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.
● Phosphodiesterase-5 inhibitors: sildenafil and tadalafil
● Sedatives/anxiolytics: midazolam and triazolam
● Acid-reducing agents: antacids (eg, aluminium and magnesium hydroxide) (recommended to separate antacid and study drug administration by 4 hours), H_2-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 IBs 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 Adverse Event 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.

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.

Dosing of cohort 2 with patients with compensated cirrhosis will only start after a DRC has reviewed all available relevant safety data when the first 6 subjects in cohort 1 completed the Week 4 visit (including but not limited to AE, Serious AE [SAE], clinical laboratory test) and no

new or unexpected events, which are considered clinically significant, are detected. Based on this review, start of dosing in cohort 2 will be notified to investigators and be opened via an interactive web response system (IWRS) by the sponsor. Enrollment in cohort 1 will be kept ongoing during the data review process.

For subjects enrolled in cohort 1, approximately 330 or 370 mL of blood will be drawn during the study, and for subjects enrolled in cohort 2, approximately 390 or 430 mL of blood will be drawn during the study, depending on the participation in the rich PK substudy.

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 Period 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 Period: -1 to +1 day.
- For visits at Weeks 2, 3, 4, and 6, of the Treatment Period: -2 to +2 days.
- For visits at Weeks 8 and 10, of the Treatment Period: -2 to +2 days (Cohort 2 only).
- For the EOT Visit: -1 to +1 day.
- For visit at Week 4 of follow-up: -3 to +3 days.

For all other scheduled visits during the 24-week Follow-up Period: -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 Period

Within 6 weeks prior to the Baseline Visit and after signing and dating the ICF, the first screening assessment should be performed. Screening assessments as indicated in the TIME AND EVENTS SCHEDULE may be split over more than one visit. After informed consent has been obtained, each subject should be registered via an IWRS (See the IWRS manual).

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 conducted and the following will be recorded for each subject: demographics, medical and surgical history, concomitant diseases, 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.

Presence or absence of cirrhosis will be determined by a fibroscan. Subjects without cirrhosis are defined as having had a fibroscan with a documented result of ≤12.5 kPA (performed 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). Subjects with compensated cirrhosis are defined as having a fibroscan (performed prior report or during Screening Period) with a documented result of >12.5 kPA or liver biopsy (prior report or during Screening Period) showing cirrhosis (eg, METAVIR score of F4 or Ishak score ≥5).

For subjects with cirrhosis, an ultrasound scan, CT scan, or MRI should be performed within 3 months prior to baseline/Day 1, with no findings suggestive of hepatocellular carcinoma.

Occurrence of clinical events related to AEs, pregnancies, and use of concomitant therapies 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 laboratory values (eg, safety laboratory or HCV RNA) that lead to exclusion will be allowed once using an unscheduled visit during the Screening Period to assess eligibility. In exceptional cases, the Screening Period 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 Period

If eligible, subjects to be treated in the study will come for the Baseline Visit (Day 1). Investigators should ensure that all study enrollment criteria have been met during screening. If, after screening but prior to the first dose of study drug, 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. After the investigator confirms that a subject met all criteria, site staff should register the subject via an IWRS on Day 1. At the Week 4 and EOT or early withdrawal visit, site staff should enter the information via an IWRS (See the IWRS manual).

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 in the morning. The timing of the baseline morning dosing should be recorded in the eCRF.

A pharmacogenomic blood sample for host *IL28B* genotyping will be collected at baseline.

Targeted physical examinations (ie, physical examinations directed at specific body systems as required based on the medical history and overall clinical presentation) (including body weight), vital sign measurements, and blood and urine samples 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-site on Day 1 and every 4 or 6 weeks as indicated in the TIME AND EVENTS SCHEDULE.

Blood sampling for the determination of the HCV RNA level (on Day 1, predose in the morning) and for viral sequencing will be performed at all scheduled visits. The HCV NS3/4A, NS5A, and NS5B regions will be sequenced pretreatment (at baseline) by default in all subjects and postbaseline in subjects not achieving SVR. Sequencing of additional samples may be triggered by the sponsor's virologist.

Hepatitis B virus DNA will be measured with PCR testing at the EOT Visit, or Treatment Withdrawal Visit, and may be evaluated at any time when there is a significant increase in the ALT or AST levels This only refers to subjects with antiHBc and/or antiHBs positive status at screening and not to subjects who have received HBV vaccine and are only antiHBs positive.

Occurrence of clinical events related to all AEs, whether serious or nonserious, pregnancies, and use of concomitant medication will be reported throughout the Treatment Period.

Echocardiography and triplicate ECG (at study approved facility) will be performed at the time points indicated in the TIME AND EVENTS SCHEDULE. Additional ECG or echocardiography may be done at any time during the study if clinically indicated in the opinion of the investigator.

All subjects will undergo sparse PK blood sampling (predose, between 2- to 4-hours postdose, and between 4- to 6-hours postdose) at the time points indicated in the TIME AND EVENTS SCHEDULE for the measurement of plasma concentrations of AL-335 (and metabolites), ODV, and SMV. At the EOT visit, intake of study drugs should take place on site when predose PK sampling (sparse and rich sampling) is performed. At Week 4, no sparse PK sample will be taken for subjects participating in the rich serial PK substudy.

In addition, rich serial PK sampling for AL-335 (and metabolites), ODV, and SMV will be performed in approximately more than 12 subjects (Cohorts 1 and 2 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 (see the TIME AND EVENTS SCHEDULE: Rich serial PK Assessments). All PK blood samples will be stored and analyzed at the discretion of the sponsor.

If study drug 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 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 Visit need to be performed.

A DRC will be established to monitor data with focus on the safety and on the general conduct of the study. Emerging safety data from this study will be reviewed at predetermined intervals.

9.1.4. Posttreatment Period (Follow-up)

All subjects will enter the 24-week Posttreatment Follow-up Period, except for subjects who withdraw consent. The latter subjects will be offered an optional safety Follow-up Visit, at which the assessments of the Week-4 Follow-up Visit need to be performed. During the Posttreatment Follow-up Period, site staff should enter the visit information via an IWRS at each scheduled visit (See the IWRS manual).

Any subject who withdraws consent during the Posttreatment Follow-up Period and/or notifies the site that 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.

Targeted physical examinations (ie, physical examinations directed at specific body systems as required based on the medical history and overall clinical presentation) (including body weight) and vital sign measurements will be performed at the Week-4 and Week-24 Follow-up Visits.

Echocardiogram and triplicate ECG will be performed at the Week-4 Follow-up Visit.

At the Week 12 Follow-up Visit, sparse PK sample will be taken at any time for the measurement of plasma concentrations of ODV.

Blood and urine samples for clinical laboratory assessments and urine pregnancy tests (for female subjects of childbearing potential) will be performed at the time points indicated in the TIME AND EVENTS SCHEDULE.

Blood sampling for determination of the HCV RNA level and for viral sequencing will be performed at all scheduled visits during follow-up. During follow-up, suspected relapse, ie, HCV RNA ≥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 nonserious, will be reported until the subject's last study visit. Pregnancies will be reported until the end of the study. The use of concomitant medication will be reported throughout the Posttreatment Follow-up Period.

9.2. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded in the Adverse Event Section of the eCRF.

All AEs, whether serious or nonserious, 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 or early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE:

9.2.1. 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, Adverse Event Reporting.

9.2.2. Clinical Laboratory Tests

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

Biochemistry samples on Day 1, Week 2, Week 4, EOT, Week 4 of follow-up, and Week 12 of follow-up must be taken after fasting for at least 8 hours. Lipid profile, insulin, and glucose are only to be assessed during visits with fasting samples.

The following tests will be performed by the central laboratory:

- Hematology Panel

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

[a] An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory.

[b] A 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 at screening, Day 1, Week 4, Week 8 (cohort 2 only), EOT, follow-up Week 4, follow-up Week 12, and follow-up Week 24, 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]	- eGFR
- B-type natriuretic peptide (BNP)[c]	

[a] The homeostasis model assessment insulin resistance (HOMA-IR) index will be derived from plasma insulin and plasma glucose (fasting for at least 8 hours) test results performed on the biochemistry sample taken after fasting at baseline, EOT, and Week 12 follow-up.

[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 Week 4 follow-up for cohort 1 and baseline, Week 2, Week 4, Week 6, Week 8, Week 10, EOT and Week 4 follow-up for cohort 2.

For each time point of the laboratory assessments, the selected central laboratory will also estimate the glomerular filtration rate.

- Urinalysis

Dipstick	Sediment (if dipstick result is abnormal)
- specific gravity	- RBCs
- pH	- WBCs
- glucose	- epithelial cells
- protein	- crystals
- blood	- casts
- ketones	- bacteria
- bilirubin	
- urobilinogen	
- nitrite	
- leukocyte esterase	

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.
- Follicle-stimulating hormone 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, HBsAg, antiHBc, antiHBs, and 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.
- Hepatitis B virus DNA will be measured with PCR testing at the EOT Visit, or Treatment Withdrawal Visit, and may be evaluated at any time when there is a significant increase in the AST or ALT levels This only refers to subjects with antiHBc and/or antiHBs positive status at screening and not to subjects who have received HBV vaccine and are only antiHBs positive.
- 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 9.2.8.1, 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 9.2.8.6.

9.2.3. Electrocardiogram

Triplicate ECGs will be performed at study approved facility 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 9.2.8.7). The mean of the triplicate ECGs need to be taken into account for decision making. The representative ECG parameters as indices are described below.

- Heart Rate
- QRS interval
- QTc interval
- QT interval
- U wave
- ST

- T wave
- PR interval

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

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

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 of inconsistent results, a technical problem with the ECG or an incorrect application of the ECG leads should be ruled out. In case of any abnormal value, the ECG recording has to be repeated.

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

9.2.4. Echocardiography

The cardiac monitoring requirements outlined in the protocol are critical and must be followed for all subjects. Repeated transthoracic echocardiography will be performed at study approved facilities to assess various echocardiographic parameters including 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 9.2.8.7).

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.

9.2.5. Vital Signs

Systolic and diastolic blood pressure and pulse 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 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 changes occurring from signing of the ICF until the subject's last study visit must be recorded in the Adverse Event Section of the eCRF.

9.2.6. Hepatitis B Virus DNA

Reactivation of HBV has been reported in association with successful treatment of hepatitis C in subjects who are infected with the HBV or patients who have a history of being infected (ie, HBsAg negative and antiHBc or hepatitis B surface antibody positive). If the drug is administered to subjects who have a history of HBV infection, attention should be paid to the occurrence of signs or symptoms related to reactivation of HBV by monitoring results of HBV markers such as HBV DNA.

Hepatitis B virus DNA will be measured by PCR testing at the EOT Visit, or Treatment Withdrawal Visit, and may be evaluated any time when there is a significant increase in the AST or ALT levels. This only refers to subjects with antiHBc and/or antiHBs positive status at screening and not to subjects who have received HBV vaccine and are only antiHBs positive (See TIME AND EVENTS SCHEDULE). In case of need of treatment for reactivated HBV, subjects will permanently discontinue the study drugs and receive a standard of care for HBV infection at the investigator's discretion.

9.2.7. 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 other 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 neurologic 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.

9.2.8. 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. Cardiac events and increased bilirubin are considered events of special interest for the 3- and 2-DAA combination programs. Photosensitivity is considered an event of clinical interest.

9.2.8.1. 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 3). 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 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]	vesiculation, moist desquamation, or ulceration OR any cutaneous event with one of the following: -elevations in AST/ALT >2×baseline value -fever >38°C or 100°F -eosinophils >1.00×10^3/µL -serum sicknesslike 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]	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.

Key: AST=aspartate aminotransferase; ALT=alanine aminotransferase; ODV=odalasvir; SMV=simeprevir; 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 3).

[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 3).

[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 and 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 the 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 nonstudy 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. The investigator should obtain a copy of the dermatologist's report for assessment of rash.

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×baseline value
  - fever >38°C or 100°F
  - eosinophils >1.00×10^3/μL
  - serum sicknesslike 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 for a Grade 3 or 4 rash 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 collected by the investigator.

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 the onset of rash. The investigator should obtain a copy of the dermatologist's report.

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 see Attachment 3.

9.2.8.2. Acute Allergic Reaction

Oral antihistamines (eg, cetirizine and 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.

Table 4: Guidelines for Subjects Developing Allergic Reactions

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.

9.2.8.3. 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. Isolated and asymptomatic cases (< 1%) of marked elevation of ALT and AST from baseline values have been reported during treatment with AL-335, ODV, and SMV. These reported cases were not accompanied by significant changes in bilirubin or other liver function markers. 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 (OATP1B1) 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.[24]

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 ALT or 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 × ULN	≥1.1 to ≤1.5 × ULN
Grade 2	>2.5 to ≤5.0 × ULN	>1.5 to ≤2.5 × ULN
Grade 3	>5.0 to ≤10.0 × ULN	>2.5 to ≤5.0 × ULN
Grade 4	>10.0 × ULN	>5.0 × ULN

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal

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).

In case of a Grade 4 bilirubin elevation, subjects should have a confirmatory measurement within 72 hours after receipt of the results. If the Grade 4 value is confirmed, all study drugs should be discontinued (Table 7).

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 ALT and/or AST Elevations

WHO Toxicity Grade	Ranges	Investigator Action
Grade 1 Grade 2 Grade 3	≥1.25 to ≤2.5 × ULN >2.5 to ≤5.0 × ULN >5.0 to ≤10.0 × 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 4	>10.0 × ULN	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. 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.

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal

Table 7: Guidelines for Subjects Developing Bilirubin Elevations

WHO Toxicity Grade	Ranges	Investigator Action
Grade 1 Grade 2 Grade 3	≥1.1 to ≤1.5 × ULN >1.5 to ≤2.5 × ULN >2.5 to ≤5.0 × ULN	May continue intake of study drugs at the investigator's discretion. Monitor for progressive increase in bilirubin levels.
Grade 4	>5.0 × ULN	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.

Key: ULN=upper limit of normal

9.2.8.4. 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, and 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.

9.2.8.5. 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.

9.2.8.6. 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 and 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×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 experiences treatment-emergent CK elevations (without a concomitant proportionate CK-MB elevation), the following treatment stopping criteria for CK elevations should be applied[31]:

- 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 ≥20×ULN, immediately redraw and repeat the test. If the repeat remains ≥20×ULN, discontinue AL-335. Continuation of ODV and SMV should be discussed with the sponsor on a case-by-case basis.
  - If CK is ≥3 – <20×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 ≥20×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 more than or equal to 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×ULN –<3×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 nonstudy drug related etiology for a CK elevation (eg, recent exercise, other clinical comorbidities [eg, endocrinal or 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×ULN, continue study medication unless follow-up CK assessments are increased to ≥20×ULN.
  - If initial CK is ≥5×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 more than or equal to 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, ECG, troponin) should be initiated.

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.

9.2.8.7. Cardiac Safety Monitoring

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

For all subjects enrolled in this study, LVEF at screening must be ≥55.0% (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 criteria[26]:

- Asymptomatic patients with no clinical evidence of congestive heart failure:
  - If the absolute decrease from baseline in LVEF is ≥10.0% (eg, 59.0% to 49.0%) and resulting in an LVEF of <50.0%, discontinue AL-335, ODV, and SMV.
  - If the absolute decrease from baseline in LVEF is >5.0% and ≤10.0%, or >10.0% and resulting in an LVEF ≥50.0%, an assessment of the subject's clinical status, including symptoms, physical examination, and other clinical parameters should be made before deciding whether to stop or continue study drugs.
- For subjects with symptoms (eg, dyspnea, orthopnea) or signs of congestive heart failure (eg, S3 gallop, pedal edema, pulmonary edema):
  - If the absolute decrease from baseline in LVEF is ≥5.0%, 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
- Troponin I assessment
- 12-lead ECG
- 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 1st degree AV block is diagnosed and
   a. The PR interval is >200 msec but ≤240 msec, study drugs can be continued. Close monitoring with weekly ECG is recommended.

b. The PR interval is >240 msec but ≤300 msec (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 msec (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 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.

3. In case the QTc value is >500 msec (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 msec 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 msec). 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.

9.2.8.8. 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/1.73m², 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/1.73m², 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.

9.2.8.9. 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 nonconfirmed 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 of "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.

9.3. Pharmacokinetics

9.3.1. Evaluations

Venous blood samples of approximately 5 mL will be collected for the measurement of plasma concentrations of AL-335 (and metabolites), ODV, and SMV at the time points specified in the TIME AND EVENTS SCHEDULE and TIME AND EVENTS SCHEDULE: Rich serial PK Assessments. At the Week 12 Follow-up Visit, venous blood samples of approximately 3 mL will be collected for the measurement of plasma concentrations of ODV.

Sparse PK Sampling

All subjects will undergo sparse PK blood sampling at Weeks 2, 4, 6, and at the EOT (Weeks 8) Visit (Cohort 1), or Weeks 2, 4, 6, 8 and at the EOT (Weeks 12) Visit (Cohort 2), predose, between 2- to 4-hours postdose, and between 4- to 6-hours postdose for the measurement of plasma concentrations of AL-335 (and metabolites), ODV, and SMV (see the TIME AND EVENTS SCHEDULE). At the EOT visit, intake of study drugs should take place on site when predose PK sampling is performed. At Week 4, no sparse PK sample will be taken for subjects participating in the rich serial PK substudy. At the Week 12 Follow-up Visit, sparse PK sample (3 mL) will be taken at any time for the measurement of plasma concentrations of ODV.

On the days of sparse PK blood sampling, the exact dates and times of PK blood sampling must be recorded according to the Laboratory Manual. The exact date and time of study drug intake on the day of the PK blood sampling and the previous day need to be recorded in the eCRF. It will be recorded whether the subjects took their study drugs in fed state (during or within 15 minutes after completion of a meal) on the day of PK blood sampling and on the previous day.

Rich Serial PK Sampling for Noncompartmental PK Analysis in the PK Subgroups

In the rich serial PK substudy, rich serial PK blood sampling will be performed in approximately more than 6 subjects in each cohort.

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 (see TIME AND EVENTS SCHEDULE: Rich serial PK Assessments). Intake of study drugs should take place on site when predose PK sampling is performed. For the intensive PK samples of the rich PK substudy, noncompartmental PK analysis of AL-335 (and metabolites), ODV, and SMV will be performed using actual sampling time points and plasma concentrations obtained from rich serial PK blood sampling at Week 4.

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 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.

A breakfast should be eaten completely within 30 minutes. The study drugs should be taken during or no later than 15 minutes after completing the breakfast.

On the days of rich PK blood sampling, the exact dates and times of PK blood sampling must be recorded according to the Laboratory Manual. The exact date and time of study drug intake on the day of the PK blood sampling and the previous day need to be recorded in the eCRF. In addition, start and end times of accompanying meal on the day of the PK sampling need to be

recorded. It will be recorded whether the 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.

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of AL-335 (and metabolites), ODV, 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.

The bioanalytical reports, including a description of the assay and a summary of the assay performance data, will be included in the final clinical study report as an addendum.

9.3.3. Pharmacokinetic Parameters

The plasma concentration-time data of AL-335 (and metabolites), ODV, and SMV from all subjects will be used for population PK (popPK) model development and/or popPK model update.

PopPK modeling will be used to describe the concentration-time profiles and estimate the exposure parameters for AL-335 (and metabolites), ODV, and SMV.

The following exposure parameters for AL-335 (and metabolites), ODV, and SMV will be derived using Bayesian feedback analysis: AUC_{24h} and predose plasma concentration (C_{0h}).

For subjects participating in the rich serial PK substudy, noncompartmental PK analysis for AL-335 (and metabolites), ODV, and SMV will be performed using actual sampling time points and plasma concentrations obtained from rich serial PK blood sampling at Week 4 for approximately more than 6 subjects in each cohort. The following PK parameters for AL-335 (and metabolites), ODV, and SMV will be derived: C_{0h}, C_{max}, t_{max}, C_{min}, AUC_{24h}, and the apparent total clearance of the drug from plasma after oral administration (CL/F).

9.4. Pharmacokinetic/Pharmacodynamic Evaluations

Relationships of AL-335 (and metabolites), ODV, and SMV population-derived exposure parameters (C_{0h} and AUC_{24h}) with SVR4, SVR12, and SVR24 and with safety endpoints may be explored graphically.

9.5. Efficacy Evaluations

9.5.1. HCV RNA Levels

Blood samples for the determination of HCV RNA levels will be taken at all scheduled visits and processed in real time. 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, a blood sample should be taken at predose in the morning. The timing of the morning dose at baseline should be recorded in the eCRF.

Results of the HCV RNA measurements will be communicated to the investigator and the sponsor 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 (see Section 6.3).

During follow-up, suspected relapse, ie, HCV RNA ≥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.

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

9.5.2. Resistance Determinations

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

Samples for viral sequencing will be taken at visits as specified in the TIME AND EVENTS SCHEDULE.

The HCV NS3/4A, NS5A, and NS5B regions will be sequenced pretreatment (at baseline) by default in all subjects and postbaseline in subjects not achieving SVR. Sequencing of additional samples may be triggered by the sponsor's virologist.

Changes in viral genotype will be evaluated by the sponsor's 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.

9.6. 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. No other analysis will be performed with this sample.

Determination of the subject's *IL28* genotype will be performed on human genomic DNA by techniques allowing amplification of the DNA and identification of the polymorphism.

9.7. 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/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at the Week 24 Follow-up Visit.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if he or she has to discontinue treatment before the end of the treatment regimen.

A subject's study treatment must be discontinued if (see Section 9.2.8 for more details):

- The investigator believes that for safety reasons or tolerability 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 9.2.8.1
- The subject has a Grade 3 or 4 allergic reaction; see Section 9.2.8.2
- The subject has a confirmed Grade 4 ALT and/or AST value that is >2 times the baseline value; see Section 9.2.8.3
- The subject has a confirmed Grade 4 bilirubin elevation; see Section 9.2.8.3
- The subject has severe worsening of hepatic disease; see Section 9.2.8.4
- The subject has a confirmed diagnosis of pancreatitis; see Section 9.2.8.5
- The subject has clinical signs suggestive of muscle injury; see Section 9.2.8.6
- The subject has evidence of cardiac toxicity, see Section 9.2.8.7
- The subject has evidence of renal toxicity, see Section 9.2.8.8.

- The subject has a Grade 4 AE or a Grade 4 laboratory abnormality at least possibly related to 1 of the study drugs; see Section 9.2.8.9

Note: For laboratory abnormalities triggering treatment discontinuation, see the toxicity management plans described in Section 9.2.8.

- 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 Posttreatment Follow-up Period. Additional unscheduled visits may be performed for safety/tolerability reasons, if needed.

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 Posttreatment Follow-up Period, the subject will be offered an optional 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 Visit need to be performed. Any subject who withdraws consent during the Posttreatment Follow-up Period and/or notifies the site that 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.

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

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). 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).

The primary analyses will be performed when all subjects have completed the Week 12 Follow-up visit (12 weeks after the end of Treatment Period) or discontinued earlier from the study. The final analysis (as secondary analysis) will be performed when all subjects have completed the last study-related visit or discontinued earlier from the study.

11.1. Subject Information

For all subjects who receive at least 1 dose of study drug, descriptive statistics will be provided.

11.2. Sample Size Determination

Since this is an exploratory study, no formal sample size calculation has been performed.

With a total sample size of 40 subjects, the probability to observe an AE with an incidence of 10.0% is 99.0%. The probability to observe an AE with an incidence of 1.0%, 2.5%, and 5.0% is 33.0%, 64.0%, and 87.0%, respectively. With 20 subjects per cohort, the probability to observe an AE with an incidence of 10.0% is 88.0%. The probability to observe an AE with an incidence of 1.0%, 2.5%, and 5.0% is 18.0%, 40.0%, and 64.0%, respectively in a cohort.

With an expected SVR rate of 90.0%, and 40 subjects in 2 cohorts combined, the corresponding 95%, 2-sided CI is 76.3% to 97.2%. With 95% SVR, the corresponding 95% CI ranges from 83.1% to 99.4%. With an expected SVR rate of 90.0%, and 20 subjects per cohort, the corresponding 95%, 2-sided CI is 68.3% to 98.8%. With 95.0% SVR, the corresponding 95% CI ranges from 75.1% to 99.9% in a cohort.

Therefore, a total sample size of approximately 40 subjects is considered sufficient to explore the safety and efficacy of the combination regimen consisting of AL-335, ODV, and SMV in this study from a clinical point of view.

11.3. Interim Analysis

No formal interim analysis will be performed; however, a DRC will be commissioned to regularly monitor the safety in interim data review.

11.4. Safety Analyses

The incidence of AEs will be summarized by body system and preferred term for each cohort and total. Changes from baseline in clinical laboratory values, vital signs, and ECG parameters will be presented descriptively. The percentage of subjects with abnormal clinical laboratory, vital signs, and ECG parameter values will be presented.

The safety analyses will be done separately for each study period (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 Period or that are a consequence of a preexisting 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 1 occurrence of the given event will be summarized by treatment cohort. In addition, comparisons between treatment cohorts 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 an 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 cohort.

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 pretreatment values.

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, and QTc interval using the following correction methods: QTcF (primary correction method)[10] and QT corrected according to Bazett's formula (QTcB).[3]

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 msec, >480 msec, or >500 msec will be summarized, as will the percentage of subjects with QTc interval increases from baseline >30 msec or >60 msec.

All clinically relevant 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 >10.0% 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 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).

11.5. Pharmacokinetic Analyses

Population PK Analysis for all Subjects

The PK samples (sparse and rich) taken from all subjects in the study (see TIME AND EVENTS SCHEDULE and TIME AND EVENTS SCHEDULE: Rich serial PK Assessments), will be used for popPK model development and/or popPK model update. PopPK analysis of plasma concentration-time data of AL-335 (and metabolites), ODV, and SMV from all subjects will be performed using nonlinear mixed-effects modeling. If deemed necessary, data will be combined with data from other studies. PopPK 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.

For each cohort, descriptive statistics, including arithmetic mean, standard deviation (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 metabolites), ODV, and SMV.

Rich Serial PK Sampling for Noncompartmental PK Analysis in the PK Subgroups

For each cohort, descriptive statistics will be provided for the plasma concentrations at each sampling time point and the PK parameters derived.

All individual concentrations at each sampling time point and all individual PK parameters will be listed. For each subject, plasma concentration-time data will be graphically presented. Similarly, graphs of the mean plasma concentration-time profiles and overlay graphs with combined individual plasma concentration-time profiles will be produced. PK parameters will be subjected to an exploratory graphical analysis. Additional analyses may be performed if deemed warranted.

11.6. Pharmacokinetic/Pharmacodynamic Analyses

Relationships of AL-335 (and metabolites), ODV, and SMV population-derived exposure parameters (AUC_{24h} and C_{0h}) with SVR4, SVR12, and SVR24 and with safety endpoints may be explored. These relationships will be presented in a graphical display.

Details will be given in a PK/pharmacodynamic (PD) analysis plan and the results of the PK/PD analysis will be presented in a separate PK/PD report.

11.7. Efficacy Analyses

The primary analyses will be performed when all subjects have reached the SVR12 time point (Week 12 Follow-up Visit) or discontinued earlier. The final analysis (as secondary analysis) will be performed when all subjects have completed the last study-related visit (SVR24 time point; Week 24 Follow-up Visit) or discontinued earlier.

The efficacy analyses will be performed on the full analysis set (FAS), defined as all subjects who received at least 1 dose of the study drug (AL-335, ODV, or SMV) and have at least

1 postbaseline efficacy measurement in the current study. Additional sensitivity analyses on efficacy may be performed after excluding subjects with early treatment discontinuation due to nonvirologic reasons or missing data at SVR4, SVR12, or SVR24 time points, as well as on the per-protocol set (PPS), defined as the FAS subjects without a prespecified major protocol deviation.

For each treatment cohort, the proportion of subjects who achieve SVR4, SVR12, and SVR24 will be calculated. A 2-sided 95% CI will be constructed around the SVR.

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

The potential association between treatment outcome and baseline subject and disease characteristics such as prior treatment history, *IL28B* genotype (rs12979860), presence of cirrhosis, HCV RNA level, and HCV geno/subtype will be explored.

Criteria for Endpoints

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.

Resistance Determination Analyses

The results of viral sequencing will be evaluated by the sponsor's virologist. Pretreatment 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 pretreatment HCV NS3/4A, NS5A, and NS5B polymorphisms on treatment outcome will be explored.

Changes in viral sequence will not be reported as AEs or SAEs.

11.8. 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.

11.9. Data Review Committee

A DRC will be established to monitor data with focus on the safety and on the general conduct of the study. Emerging safety data from this study will be reviewed at predetermined intervals.

To conduct this study carefully in light of securing subjects' safety, dosing of cohort 2 with patients with compensated cirrhosis will only start after a DRC has reviewed all available relevant safety data when the first 6 subjects in cohort 1 completed the Week 4 visit (including but not limited to AE, SAE, clinical laboratory test) and no new or unexpected events, which are

considered clinically significant, are detected. DRC may require to review data of further patients before deciding about the start of dosing in cohort 2.

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).

The DRC will consist of at least 1 medical expert in the relevant therapeutic area, 1 cardiologist (for the review and interpretation of any cardiac safety data) and at least 1 statistician. The DRC responsibilities, authorities, and operating procedures 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 noninvestigational) 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 noninvestigational) product, whether or not related to that medicinal (investigational or noninvestigational) 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 European Union 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 and addenda.

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 following 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 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)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the Serious Adverse Event page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last visit. Serious adverse events, including those spontaneously reported to the investigator 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 an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

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
- Any other information that is required to do an emergency breaking of the blind

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 an 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 an 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 an 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: Rich serial PK Assessments).

The cause of death of a subject in a study, whether or not the event is expected or associated with the study drug, is considered an SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form from the time a signed and dated ICF is obtained until the end of the study. 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. 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 as noted above.

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 in 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 in 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.[16,18]

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. [19,20]

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 and its addendum for the list of excipients.[21,22]

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 drugs 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

The study drugs must be stored in a secure area and administered only to the subjects enrolled into this clinical study, in accordance with the conditions specified in this protocol.

Refer to the pharmacy manual/study site investigational product and procedures 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:

- Investigator's Brochure's for AL-335, ODV, and SMV, and their addenda
- Site investigational product procedure manual
- Echocardiography manual
- ECG manual
- Laboratory manual
- Medication diaries
- Electronic Data Capture (eDC) Manual
- Sample ICF
- Contact information page
- IWRS manual

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 ICF (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, unless required locally), 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, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed. The physician may also recontact the subject for the purpose of obtaining consent to collect 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 must be given to the subject.

Where local regulations require, a separate ICF may be used for the required DNA (*IL28B* genotype) component of the study.

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, 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 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 poststudy 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 10.2)

16.2.6. Country Selection

This study will only be conducted in Japan, where the intent is to launch the developed product.

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 nonacceptance, 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 IEC/IRB (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 listed in the Contact Information page(s), which will be provided as a separate document. 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 enrolled 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 documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care 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.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods 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
- Blood pressure and pulse rate
- Height and weight

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.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through

the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF. Study-specific data will be transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the study site.

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 documents. Data must be entered into eCRF in English. Study-site personnel must enter the data into the eCRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the eCRF, this can be done in either of the following 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, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. 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 eCRF 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 eCRF 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 postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). 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 documents (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 documents 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/End of Study

The study will be considered to be 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 AL-335 ODV, and 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 AL-335 ODV, and 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 and laboratory data from the selected laboratory 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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Attachment 1: WHO Scale for Determining the Severity of Adverse Events

February 2003

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/mm³	750-999/mm³	500-749/mm³	<500/mm³
Platelets	75,000-99,000/mm³	50,000-74,999/mm³	20,000-49,999/mm³	<20,000/mm³
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 (nonfasting 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	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

Item	Grade 1	Grade 2	Grade 3	Grade 4
albumin)				arrhythmia or tetany
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 <80.0%-70.0% 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 <25.0% (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 25.0%-50.0%	normal activity decreased >50.0% 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]

Key: FEV_1=forced expiratory volume in 1 second; IV=intravenous; LLN=lower limit of normal; R_x=therapy; ULN=upper limit of normal

[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 mm Hg	≤90 mm Hg
Grade 1 or mild	-	>90 mm Hg to <100 mm Hg	>140 mm Hg to <160 mm Hg
Grade 2 or moderate	-	≥100 mm Hg to <110 mm Hg	≥160 mm Hg to <180 mm Hg
Grade 3 or severe	-	≥110 mm Hg	≥180 mm Hg
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 2nd degree AV block OR Ventricular pause >3.0 sec	Complete AV block

*Revised by the sponsor.

Attachment 3: 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]	• 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.**	• 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).	• 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 grade 4 rash (as soon as possible after onset of rash). Biopsy at the dermatologist's discretion for grade 3 rash.
Day 1			• Follow-up visit (on-

	Grade 1 Rash	Grade 2 Rash	Grade 3 or 4 Rash
			site) **REQUIRED**. • Assessment of safety blood sample by local laboratory **REQUIRED**.
Further Visits	• 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.	• Appropriate unscheduled Follow-up Visits at the investigator's discretion until resolution of rash.[b] • At these visits, safety blood samples **must** be taken.	• 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.

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.

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): Ei Fujikawa

Institution: Janssen Pharmaceutical K.K.

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.