Alios BioPharma, Inc
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Protocol Number: AL-335-604

A Phase 2a, Open-Label Study to Evaluate the Safety, Pharmacokinetics and Efficacy of the Combination of AL-335 and Odalasvir, with or without Simeprevir, in Treatment-Naïve Subjects with Genotype 1, 2 or 3 Chronic Hepatitis C infection with or without compensated Child Pugh A Cirrhosis

Drug Names: AL-335, ACH-3102 (odalasvir), simeprevir

IND Number: This is a Non-IND Study

EudraCT Number: 2016-002845-46

Date: 03 May 2017

Version 10.0

Contact Information

For up-to-date contact information, see Study Binder: Emergency Contact Sheet.

All serious pretreatment and treatment-emergent adverse events, including pregnancies and suspected pregnancies,[1] occurring from the time of consent up to 6 months after study drug administration is completed, regardless of relationship to study drug, must be reported via fax to the Sponsor's designee within 24 hours of knowledge of the event.

Please fax all Serious Adverse Event Forms to:

CRO Pharmacovigilance	
SAE Fax Number:	[redacted]
SAE e-mail address:	[redacted]
Telephone contact: [redacted]	[redacted]

Sponsor's Medical Monitor	[redacted] **MD**	
Sponsor's Medical Monitor Telephone contact:	Mobile: [redacted] Desk: [redacted]	
SAE Fax Number:	[redacted]	Alios BioPharma
SAE e-mail address:	[redacted]	
Please also FAX to the recipient identified in the study reference binder.		

Any fatal or life-threatening event, adverse event which triggers study treatment stopping criteria (Section 4.7.1), pregnancy or suspected pregnancy must also be reported within 24 hours by telephone.

[1] See Sections 7.1.1 and 7.1.3 for the definitions of *pretreatment adverse event* and *serious adverse event. Pregnancy itself does not constitute an adverse event.*

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Abbreviations

Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0-\tau}$	Area under the plasma concentration-time curve during the dosing interval τ
BMI	Body mass index
BP	Blood pressure
CHC	Chronic hepatitis C
CK	Creatine kinase
C_{max}	Maximum measured drug concentration
CRF	Case Report Form
CYP	Cytochrome P450
EC	Ethics Committee
ECG	Electrocardiogram
EC_X	X% maximal effective concentration
EF	Ejection fraction
EOT	End of treatment
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GT	Genotype
HAV	Hepatitis A virus immunoglobulin
IgM	Immunoglobulin M
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	Heart rate
IC_{50}	50% inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalization Ratio
IRB	Institutional Review Board
kPa	Kilo Pascal
LFC	liquid-filled capsule
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	No-observed-adverse-effect level
NS	Nonstructural protein
ODV	Odalasvir
OTC	Over the counter
PegIFN	Pegylated interferon
P-gp	P-glycoprotein
PK	Pharmacokinetic
PT	Prothrombin time
PTT	Partial thromboplastin time

Term	Definition
qd	Once daily
qod	Every other day
RNA	Ribonucleic acid
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SMV	Simeprevir
SOC	System Organ Class
SUSAR	Serious and Unexpected Adverse Reaction
SVR	Sustained virologic response
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach the maximum plasma concentration
ULN	Upper limit of normal
WHO	World Health Organization

List of Study Drugs and Metabolites

Compound Number	Alternative Compound ID	Comment
AL-335	ALS-022335	Investigational drug; *Sp* isomer; phosphoramidate prodrug of the uridine nucleoside analog ALS-022227
ALS-022227	–	parent uridine nucleoside analog, major metabolite of AL-335 in systemic circulation
ALS-022235	–	5'-triphosphate of ALS-022227 (NTP), active intracellular entity
ALS-022399	–	major metabolite of AL-335 in systemic circulation
Odalasvir	ACH-0143102; ODV	Investigational drug; HCV nonstructural protein 5A (NS5A) inhibitor
Simeprevir	SMV	an oral HCV protease inhibitor for the treatment of hepatitis C

NTP: nucleoside triphosphate.

Definitions

End of study:	Week 24 Virology Follow-up Visit either after last planned dose date or, if virologic failure occurred prior to this date, after time of failure for the last subject treated
End of treatment (EOT)	Completion of dosing or premature discontinuation of treatment, whichever is earlier
On-treatment Virologic Response	HCV RNA results satisfying a specified threshold. The following thresholds will be considered at any timepoint: <LLOQ undetectable <LLOQ detectable <LLOQ undetectable/detectable
Sustained Virologic Response (SVR)	The subject has HCV RNA <LLOQ detectable or undetectable 4, 8, 12, 18 or 24 weeks after the actual end of study drug treatment.
Failure (no SVR12)	Subjects who did not achieve SVR12, including: • on-treatment failure (see below) • post-treatment failure, includes subjects with: o viral relapse (see below); o missing HCV RNA at timepoint of SVR12.
On-treatment Failure	Subjects who did not achieve SVR12 and with confirmed HCV RNA ≥LLOQ at the actual end of study drug treatment. Includes subjects: • With viral breakthrough, defined as a confirmed increase of >1 $\log_{10}$ in HCV RNA from nadir, or confirmed HCV RNA of >100 IU/mL in subjects whose HCV RNA had previously been <LLOQ while on treatment. • With Inadequate virologic response defined as <1 $\log_{10}$ decline from baseline in HCV RNA after 4 weeks of treatment • Who do not experience viral breakthrough or inadequate virologic response and have confirmed HCV RNA ≥LLOQ at the actual end of study drug treatment (e.g., completed study drug treatment, discontinued due to adverse events, withdrawal of consent).
Viral Relapse	Subjects who did not achieve SVR12, with HCV RNA <LLOQ at the actual end of study drug treatment and confirmed HCV RNA ≥LLOQ during follow up.

HCV: hepatitis C virus; LLOQ: lower limit of quantitation; RNA: ribonucleic acid.

Synopsis

A Phase 2a, Open-Label Study to Evaluate the Safety, Pharmacokinetics and Efficacy of the Combination of AL-335 and Odalasvir, with or without Simeprevir, in Treatment-Naïve Subjects with Genotype 1, 2 or 3 Chronic Hepatitis C infection with or without compensated Child Pugh A Cirrhosis

Protocol No. :	AL-335-604
Phase:	2a
Study Drugs:	AL-335, Odalasvir (ODV), Simeprevir (SMV)
IND Number:	This is a non-IND study
EudraCT No.:	2016–002845–46
Background Therapy:	None
Comparator:	None
Indication:	Chronic hepatitis C (CHC)

Study Design:	This open-label study will assess the safety, pharmacokinetics and efficacy of an orally administered combination of AL-335 and ODV with or without SMV in treatment-naïve and treatment experienced subjects with CHC infection. Up to 320 subjects with CHC genotype (GT) 1, 2, or 3 infection will be enrolled to receive up to 1200 mg once daily (qd) of AL-335 in combination with ODV up to 50 mg qd or qod, with or without up to 150 mg qd SMV.
	
	Based on emerging safety, pharmacokinetic (PK), and efficacy data, the following study parameters may be changed for ongoing and future cohorts after obtaining agreement from the Sponsor and the Principal Investigator:
	
	• Treatment duration: 4-12 weeks
	• Dose levels:
	  ○ AL-335: 400-1200 mg qd
	  ○ ODV: 25-50 mg (dosed either qd or every other day [qod])
	  ○ SMV: 75-150 mg qd (if evaluated in a cohort)
	• Genotype: GT1 and/or GT2 and/or GT3; Cohorts may also be limited to specific subtypes (e.g., GT1a only) or may include all subtypes.
	• Cohort size: 10-20 subjects. In ongoing cohorts in which a dosing regimen is modified (e.g., treatment duration is extended) due to apparently insufficient efficacy/safety, the cohort size may be increased such that 20 subjects at the final dosing regimen are enrolled in that cohort.
	• Population: Treatment-naïve non-cirrhotic HCV-infected subjects

and treatment naïve or treatment experienced HCV-infected subjects with compensated cirrhosis (decompensated cirrhosis prohibited)

- Viral load: A viral load threshold may be included in determining eligibility for a cohort if higher viral loads are projected to have unacceptable efficacy. This threshold may be derived from emerging data (e.g., prior cohorts), medical literature, etc.
- Number of cohorts: Up to a total of 16 cohorts (maximum N=320 subjects) with the above defined constraints may be enrolled.

The planned study design is depicted in Figure 1.

Figure 1– Study Design

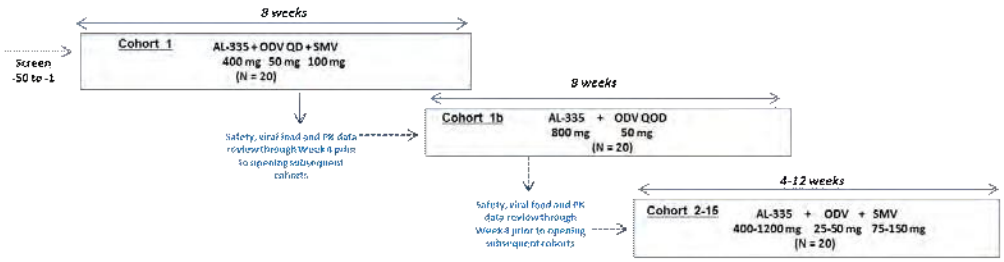

**Figure depicts range of permissible durations, total daily doses for each drug for cohorts 2-15. Based on emerging safety, pharmacokinetic, and efficacy data, the following study parameters may be changed for a given cohort after obtaining agreement from the Sponsor and the Investigator:

- Treatment duration: 4-12 weeks
- Doses
  - AL-335: 400-1200 mg
  - Odalasvir: 25-50mg (QD or QOD)
  - Simeprevir: 75-150 mg (if evaluated in a cohort)
- Genotype: Any combination of GT 1, 2 and 3
- Cohort size: 10-20 subjects. In ongoing cohorts in which a dosing regimen is modified (e.g. treatment duration is extended) due to apparently insufficient efficacy/safety, the cohort size may be increased such that 20 subjects at the final dosing regimen are enrolled in that cohort.
- Population: Treatment-naïve non-cirrhotic HCV-infected subjects and treatment naïve or treatment experienced HCV infected subjects with compensated cirrhosis (decompensated cirrhosis prohibited)
- Viral load: A viral load threshold may be included in determining eligibility for a cohort if higher viral loads are projected to have unacceptable efficacy. This threshold may be derived from emerging data (e.g. prior cohorts), medical literature, etc.

The initial 8-week treatment cohort (Cohort 1) will consist of at least 50% HCV GT1a. After 4 weeks of treatment in the 8 week treatment cohort, safety, viral load and available PK data from at least 16 of 20 subjects will be reviewed by the Sponsor in consultation with the Principal Investigator prior to initiation of enrollment of additional cohorts. If necessary, the review may be extended to include the full PK data set from the Week 2 intensive PK assessment.

After the initial cohort (Cohort 1), subsequent cohorts may be enrolled concurrently or in a staggered fashion. Effective as of approval of protocol version 7, prior to evaluating a given treatment regimen in subjects with cirrhosis or for a shorter duration, efficacy, safety, and available PK data for that treatment regimen in subjects without cirrhosis and/or for a longer

duration will be reviewed. Specifically, data from at least 10 subjects at the SVR4 time point will be reviewed and, if acceptable (see Section 4.8), subsequent cohorts evaluating shorter durations and/or subjects with cirrhosis will be initiated. The timing of initiating enrollment in these subsequent cohorts will be coordinated such that SVR12 data from at least 10 subjects in the earlier cohort will be available before the end of treatment visit occurs for the first subject in the subsequent cohort. This timing is designed to enable extension of the treatment duration in the subsequent cohort if the earlier cohort is determined to have insufficient efficacy.

Based on data available as of 17 February 2017, the following cohorts have been completed, initiated or are planned (Synopsis Table 1). Available viral kinetic (VK) data are also included in the table. Cohorts 6 through 12 are currently open for enrollment or planned at the time of this protocol finalization. The cohort regimens will only change if emerging data requires they be altered for safety purposes. Some planned cohorts may not be enrolled if emerging data are not supportive or suggest the cohort is not necessary to achieve the study's objectives.

Synopsis Table 1. Completed, Initiated, and Planned Cohorts^ with Available VK Data

Cohort #	GT	Cirrhosis	AL-335 dose (mg)	ODV dose (mg)	SMV dose (mg)	Duration (weeks)	Cohort Status	Number (%) achieving SVR
1	1	N	400	50 QD	100	8	Through SVR24	20/20 (100%), SVR24
1b	1	N	800	50 QOD	--	8	Through SVR24	18/20 (90%), SVR24
2	1	N	800	50 QOD	75	8	Through SVR24	20/20 (100%), SVR24
3	1	N	800	50 QOD	75	6	Through SVR24	20/20 (100%), SVR24
4	1	N	800	50 QOD	--	8 (N=5) 12 (N=8)	Through SVR24 Through SVR12	3/5 (60%), SVR24 7/8 (88%), SVR12
5	3	N	800	50 QOD	75	8 (N=5) 12 (N=14)	Through SVR24 Through EOT	0/5 (0%), SVR24 13/14 (93%), EOT
6	1	Y	800	50 QOD	75	8	Enrolling (N=11)	9/10 (90%), SVR12*
7	1	Y	800	25 QD	75	8	Screening/Planned	N/A
8	1	Y	800	25 QD	75	8	Screening/Planned	N/A
9	1	Y	800	25 QD	75	12	Screening/Planned	N/A
10	1	Y	800	25 QD	75	12	Screening/Planned	N/A
11	2	Y	800	25 QD	75	12	Screening/Planned	N/A
12	2	Y	800	25 QD	75	8	Screening/Planned	N/A
12-15	TBD							

* Subject 11 has completed treatment. SVR visit results pending.

^N=10-20 per cohort; in any ongoing cohorts in which a dosing regimen is modified (e.g., treatment duration is extended) due to apparently insufficient efficacy/safety, the cohort size may be increased such that 20 subjects at the final dosing regimen are enrolled in that cohort

This protocol permits enrollment of up to 16 cohorts. The maximum permissible enrollment in this study is up to 320 subjects.

Safety and tolerability will be evaluated on an ongoing basis through

	assessment of adverse events (AEs), blood and urine sample analyses, collection of electrocardiograms (ECG), echocardiograms, vital signs and physical examinations. PK data will be routinely reviewed as it becomes available. All enrolled subjects will be monitored from Day 1 through end of follow up for on treatment failure or relapse as defined by the criteria outlined in Sections 8.2.2–8.2.4, respectively. Where necessary, the Sponsor will offer appropriate retreatment within a separate protocol or, if the subject is unable or unwilling to participate in that trial, the Sponsor will provide reimbursement for locally available HCV treatment for any subjects that experience on treatment failure or relapse, subject to local regulations. See Section 2.0, Study Design, for additional information. PK samples will be obtained at a single time point prior to dosing at all routine study visits while subjects are receiving study medication as well as at Weeks 3 and 6, 2-4 hours postdose, and at Weeks 4 and 8, 6-8 hours postdose. In addition, for a subgroup of up to 250 subjects, additional PK samples will be obtained at Week 2 for all treatment groups. See Section 6.0 for details of Study Procedures.
Objectives:	The primary objective of this study is as follows: • To evaluate the safety and tolerability of AL-335 in combination with ODV with or without SMV in subjects with GT1 or GT2 or GT3 CHC infection The secondary objectives of this study are as follows: • To evaluate the efficacy of treatment with AL-335 in combination with ODV±SMV in subjects with GT1 or GT2 or GT3 CHC infection • To evaluate the pharmacokinetics of AL-335 (and metabolites), ODV±SMV in plasma • To evaluate the viral kinetics of HCV RNA in subjects with GT1 or GT2 or GT3 CHC infection treated with AL-335 in combination with ODV±SMV • To evaluate the effect of baseline host and disease-related characteristics on treatment outcome • To evaluate the impact of the presence of a nonstructural protein (NS) 3 polymorphism (e.g., Q80K; SMV-containing arms only) and/or NS5A and NS5B polymorphisms at baseline on treatment outcome • To evaluate the viral resistance profile after ≤12 weeks administration of AL-335 in combination with ODV±SMV.

Primary Endpoint:	• Safety data, including but not limited to tabulation of AEs, physical exam, vital signs, 12-lead ECGs, echocardiograms, and clinical laboratory results (including chemistry, hematology, and urine)
Secondary Endpoints:	• The proportion of subjects who have a sustained virologic response (SVR; i.e., HCV RNA concentration below the lower limit of quantitation [<LLOQ; <15 IU/mL]) at 4, 8, 12, 18 and 24 weeks after the last actual dose of treatment • PK parameters for AL-335 (and metabolites), ODV and SMV in plasma • The proportion of subjects who experience virologic relapse during the follow-up period. • The proportion of subjects who have on treatment failure while receiving study medication • Viral kinetics, as determined at different timepoints during treatment by the proportion of subjects who achieve - HCV RNA <LLOQ undetectable - HCV RNA <LLOQ • Time to achieve undetectable HCV RNA and <LLOQ HCV RNA • The amino acid sequence of the NS5A, NS5B and NS3/4A proteins at baseline and post-baseline in subjects who fail treatment • Effect of various baseline and host disease-related characteristics on treatment outcome
Duration of Treatment and Study Period:	Up to 43 weeks (from screening through study completion) for each enrolled subject as follows: • Screening: Up to 50 days • Study Period: Up to 12 weeks • Follow-up: Up to 24 weeks after completion of study medications
Number of Sites and Location:	Up to 50 sites globally
Sample Size:	Up to 320 treatment-naïve and treatment experienced subjects with CHC infection will be enrolled in up to 16 cohorts. Since this is an exploratory study, no formal sample size calculation has been performed. A total sample size of 10-20 subjects/cohort is considered sufficient to explore the safety, pharmacokinetics, and efficacy of the possible study regimens in various HCV-infected subpopulations (e.g., GT1, compensated cirrhosis, etc).

Inclusion Criteria:

Main Inclusion Criteria for All Subjects:

1. Subject has provided written consent.
2. In the Investigator's opinion, the subject is able to understand and comply with protocol requirements, instructions, and protocol-stated restrictions and is likely to complete the study as planned.
3. Male or female, 18–70 years of age.
4. Body mass index (BMI) 18–35 kg/m^2, inclusive.
5. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin) pregnancy test at screening.
6. Female subjects must either:
   - not be of childbearing potential defined as:
     i. Postmenopausal for at least 12 months (i.e., 2 years of amenorrhea without an alternative medical cause) and a serum follicle stimulating hormone (FSH) level in the postmenopausal range (per reference laboratory), OR
     ii. Surgically sterile (e.g., underwent total hysterectomy, bilateral oophorectomy, or bilateral tubal ligation/bilateral tubal clips without reversal operation), or otherwise incapable of becoming pregnant,
   - OR
     i. be of childbearing potential AND
     ii. not heterosexually active (e.g., abstinent or homosexual) from screening until 6 months after study drug administration (or longer, if dictated by local regulations), OR
     iii. if heterosexually active
       - have a vasectomized partner (confirmed sterile per verbal account of the subject), OR
       - using an acceptable method of birth control from screening and agree to continue to use the same method of contraception throughout the study and for 6 months after study drug administration (or longer, if dictated by local regulations). Acceptable methods of birth control include: oral hormone-based contraceptives, an IUD, being either hormonal (i.e., IUS) or non-hormonal, other non-oral hormone-based contraception methods (e.g., injectable, implants, transdermal system, vaginal ring), or a double-

barrier method (eg, male condom + either a diaphragm or cervical cap with or without spermicide). Condom use by male partners with reproductive potential is required in all circumstances except when female subjects are using acceptable birth control methods which are long term in nature and do not require high degrees of compliance (e.g. IUDs, depot-form injectables, implants).
    - See also the NOTES regarding contraception considerations that apply to men and women at the bottom of Inclusion #7

7. Male subjects must either:
    - be surgically sterile (had a vasectomy), or otherwise incapable of fathering a child, OR
    - not be heterosexually active (e.g., abstinent or homosexual) from enrollment (Day 1) in the study until at least 6 months after study drug administration, OR
    - if heterosexually active:
        - have a partner who is postmenopausal (2 years amenorrhea), surgically sterile (e.g., has had a total hysterectomy, bilateral oophorectomy, or bilateral tubal ligation/bilateral tubal clips without reversal operation), or otherwise incapable of becoming pregnant OR
        - be practicing an acceptable method of birth control from enrollment in the study (Day 1) and agree to continue to use the same method of contraception throughout the study and for at least 6 months after study drug administration (or longer, if dictated by local regulations). An acceptable method of birth control for male subjects is a double-barrier method (e.g., male condom+either diaphragm or cervical cap with or without spermicide).

NOTE 1: Male subjects with a female partner who uses hormonal contraceptives (oral, injectable, implants) or a hormonal (IUS) or non-hormonal IUD and male subjects who are vasectomized or otherwise incapable of fathering a child are not required to use additional contraceptive methods.

NOTE 2: 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 3: A male and female condom should not be used together due to risk of breakage or damage caused by latex friction.

NOTE 4: Contraceptive use by men and 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

8. Subjects must agree to refrain from sperm/egg donation from start of dosing through 6 months after the completion of study drug administration.
9. GT1a or 1b or GT2 or 3 CHC, depending on cohort, with positive HCV antibody and a positive HCV RNA at screening including documentation of CHC infection for at least 6 months. Genotype testing must occur at a screening visit. NOTE: GT1 patients are eligible for inclusion even if they cannot be successfully subtyped unless a specific subtype is required for a cohort.
10. Screening HCV RNA viral load ≥50,000 IU/mL, except for subjects with compensated cirrhosis (Child-Pugh Class A) who may have HCV RNA viral load ≥10^4 IU/mL.
11. Treatment naïve (i.e., no prior exposure to any approved or investigational drug(s) including direct-acting antivirals, and interferon-based treatment regimens) or, in subjects with cirrhosis, treatment experienced (defined as subjects who experienced virologic relapse after receiving a full course of pegylated interferon+ribavirin (peg/riba) treatment). Prior use of any direct acting antiviral in combination with peg/riba is not permitted.
12. Fibroscan, collected within 6 months of baseline visit, with liver stiffness score ≤12.5 kPa to be eligible (except for subjects with cirrhosis, see below).
    - Subjects with compensated cirrhosis must meet the Child-Pugh Class A definition (see Appendix G) and at least one of the following criteria:
      i. Liver biopsy result indicating the presence of cirrhosis (e.g., Metavir F4; Ishak >5) or
      ii. Fibroscan evaluation with a liver stiffness score >12.5 kPa
13. Subject is otherwise in good health as deemed by the investigator, based on the findings of a medical evaluation including medical history, physical examination, laboratory tests and ECG.
14. Willing to avoid prolonged sun exposure and use of tanning

	devices while taking SMV and through 4 weeks of follow up. Subjects should also be advised to use a broad-spectrum sunscreen and lip balm of at least sun protection factor >30 to help protect against potential sunburn.
Exclusion Criteria:	Subjects will be ineligible for this study if they meet **any** of the following criteria: 1. Pregnant, planning on becoming pregnant (during treatment and up to 6 months after the EOT), or breast-feeding female subject, or male subject whose female partner is pregnant or planning on becoming pregnant (during treatment and up to 6 months after the EOT) 2. Other than CHC with or without compensated cirrhosis, clinically significant cardiovascular, respiratory, renal, gastrointestinal, hematologic, neurologic, thyroid or any other medical illness or psychiatric disorder, as determined by the Investigator and/or Sponsor's Medical Monitor. 3. History or other clinical evidence of significant or unstable cardiac disease (e.g., angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia, coronary heart disease, and/or clinically significant ECG abnormalities), moderate to severe valvular disease or uncontrolled hypertension at screening. 4. Screening echocardiogram ejection fraction <55% or any other echocardiographic finding suggestive of clinically relevant cardiomyopathy. 5. Creatinine clearance of <60 mL/min (Cockcroft-Gault). 6. Positive test for HAV IgM, HBsAg, or HIV Ab. 7. Abnormal screening laboratory results that are considered clinically significant by the investigator. 8. History of clinical hepatic decompensation, e.g., variceal bleeding, spontaneous bacterial peritonitis, ascites, hepatic encephalopathy or active jaundice within the last year. 9. Any condition that, in the opinion of the investigator, would compromise the study's objectives or the well-being of the subject or prevent the subject from meeting the study requirements. 10. Participation in an investigational drug trial or having received an investigational vaccine within 30 days or

5 half-lives (whichever is longer) prior to study medication.

11. Clinically significant abnormal screening ECG findings (e.g., PR >200 msec, QRS interval >120 msec or corrected QT interval (QTc) >450 msec for male subjects and >470 msec for female subjects), based on an average of triplicate ECGs. Any evidence of heart block or bundle branch block is also exclusionary.

12. History or family history of abnormal ECG intervals, for example prolonged QT syndrome (torsade de pointes) or sudden cardiac death.

13. The subject has a positive prestudy drug screen, including methadone unless the drug is prescribed by the subject's physician. The list of drugs that should be screened for includes amphetamines, barbiturates, cocaine, opiates, phencyclidine (PCP), and benzodiazepines. Drug use without a physician prescription may be permitted on a case by case basis after review by the Sponsor in consultation with the investigator.

14. Laboratory abnormalities including:
    - Hematocrit <0.34
    - White blood cell counts <3,500/mm^3 (<1,000/mm^3 for subjects with compensated cirrhosis)
    - Absolute neutrophil count <1,000/mm^3 (<750/mm^3 for subjects with compensated cirrhosis)
    - Platelets ≤120,000/mm^3 (platelets <70,000/mm^3 for subjects with compensated cirrhosis)
    - Glycosylated hemoglobin (HbA1C) >55 mmol/mol or 7.2%
    - Prothrombin time ≥1.5 × ULN
    - Albumin ≤32 g/L, bilirubin ≥1.5 mg/dL at screening (subjects with documented Gilbert's disease allowed)
    - Serum ALT concentration ≥5× ULN
    - CK >1.5× ULN

    A single repeat laboratory evaluation under appropriate conditions (e.g., fasted, no antecedent exercise) is allowed for eligibility determination.

15. Any condition possibly affecting drug absorption (e.g., gastrectomy or other significant gastrointestinal tract surgery, such as gastroenterostomy, small bowel resection, or

	active enterostomy). 16. Clinically significant blood loss or elective blood donation of significant volume (i.e., >500 mL) within 60 days of first dose of study drug; >1 unit of plasma within 7 days of first dose of study drug. 17. Evidence of clinically relevant active infection that would interfere with study conduct or its interpretation. 18. History of regular alcohol intake >10 standard drinks per week of alcohol for females and >15 standard drinks per week for males (one unit is defined as 10 g alcohol) within 3 months of the screening visit. 19. The use of prohibited medications, including prescription, over-the-counter (OTC) medications, herbal medications, inducers or inhibitors of CYP450 enzymes or drug transporters (including P-gp) within 14 days prior to the first dose of study medication is excluded, unless previously approved by the Sponsor's Medical Monitor. NOTE: Chronic medication use is permitted so long as they are medically necessary, deemed acceptable by the Principal Investigator and Medical Monitor, and not Prohibited Medications (see Section 5.12). 20. Hypersensitivity to the active substances (including sulfa allergy) or to any of the excipients of AL-335, ODV or SMV. 21. Evidence on recent (within 6 months) liver ultrasound of hepatic mass or lesion concerning for malignancy (subjects with cirrhosis only).
Dosage Form and Strength:	AL-335 will be supplied as 100-mg and 400-mg tablets. ODV will be supplied as film-coated 25-mg and 50-mg tablets. SMV will be supplied as 75-mg, 100-mg and150-mg capsules.
Dose Regimen:	Study medications will be administered (see Section 6.0) under fed conditions. Subjects will be advised to take oral qd doses of AL-335 and SMV (if applicable), and qd or qod doses of ODV, with approximately 250 mL of room temperature, non-carbonated water. The treatment duration, dosing frequency, doses, genotypes, cohort size, and CHC subpopulation in a given cohort may be modified based upon review of emerging safety, efficacy and/or PK data (see Study Design, above). Cohorts 2–15 may or may not include SMV. Mean projected plasma exposures of ALS-022399, ALS-022227, and ODV at the doses selected in study cohorts will not exceed

	no-observed-adverse-effect level (NOAEL) exposures obtained from nonclinical toxicology studies. SMV doses will not exceed the approved dose.
Predosing and Concomitant Medications:	None

1.0 BACKGROUND AND RATIONALE

1.1 Background Information on Hepatitis C Virus

There are approximately 170 million people or 3% of the world's population infected with hepatitis C virus (HCV) (World Health Organization, WHO) with more than 365,000 deaths per year resulting from long-term complications (Perz et al. 2006). Chronic hepatitis C (CHC) is the most common chronic liver disease in the United States and Europe and is the leading cause for liver transplantation in these regions. CHC infection results in a significant risk of developing long-term complications such as cirrhosis and hepatocellular carcinoma, although estimates for the progression rates vary. The risk of hepatic decompensation in subjects with cirrhosis is approximately 5% per year (Poynard et al. 1997) and the 5-year survival rate after decompensation is around 50% (Planas et al. 2004).

1.2 AL-335 Background

AL-335 is a uridine base nucleoside monophosphate prodrug (or nucleotide analog) being developed as an orally administered anti-HCV therapeutic. AL-335 retains potent antiviral activity against all genotypes, including most HCV replicons that show resistance to other direct-acting antiviral agents. AL-335 is efficiently converted to ALS-022235, the active NTP, in human hepatocytes.

Neither AL-335 (IC_{50} >100 µM at 37°C) nor its metabolites (IC_{50} >100 µM) blocked the human ether-a-go-go gene (hERG) potassium channel current at physiologically relevant concentrations. In the in vivo safety pharmacology studies, AL-335 did not have any central nervous system-related effects or respiratory effects in rats nor cardiovascular changes in dogs up to the highest doses tested (1000 mg/kg/day). In 14-day and 91-day repeat-dose toxicity studies, AL-335 was well tolerated in rats and dogs with no changes in hematology, serum chemistry, or histopathology up to 1000 mg/kg/day, the highest dose tested (the no-observed-adverse-effect level [NOAEL]). In rats, exposure to AL-335 was very low due to rapid degradation by esterases; however, plasma exposures of the metabolites ALS-022399 and ALS-022227 increased with dose. In dogs, plasma exposure to all 3 analytes increased with increase in dose with no significant accumulation upon repeated dosing. At the NOAEL of 1000 mg/kg/day following 91 days of repeated dosing, the plasma exposures (AUC_{0-24}) in rats and dogs, respectively, were below the limit of quantitation (BQL) and 2690 ng•h/mL for AL-335, 1570 and 15,700 ng•h/mL for ALS-022399, and 5980 and 51,900 ng•h/mL for ALS-022227.

In rat and rabbit embryo-fetal developmental studies, preliminary data indicate that AL-335 did not cause any changes in intrauterine growth or survival or fetal morphology at any dosage level up to the highest doses of 1000 and 300 mg/kg/day, respectively. In addition, preliminary data also indicated that AL-335 did not have any adverse effects/disturbances in the reproductive process from pre-mating to conception and from conception to implantation in rats up to the highest dose of 1000 mg/kg/day. This included identification of deficits in estrous cycling, tubal transport, implantation, and development of the pre-implantation stages of the embryo in the female and functional reproductive effects (alterations in libido and epididymal sperm maturation) in the male.

AL-335 is metabolized by esterases. It has demonstrated a low inhibition potential to CYPP450 enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (IC_{50} >26 µM). The metabolites, ALS-022399 and ALS-022227, also had low inhibition potentials to the above enzymes with IC_{50} >48 µM for ALS-022399 and IC_{50} >40 µM for ALS-022227. AL-335 and metabolites are not expected to cause drug–drug interaction with other drugs that are metabolized by CYPP450 enzymes. AL-335 is a substrate of P-glycoprotein (P-gp) transporter, but does not have the potential to inhibit P-gp or OATP1B1/1B3. The metabolites, ALS-022399 and ALS-022227, are neither substrates nor inhibitors of P-gp, OATP1B1/1B3, OAT1/3 and OCT2 transporters.

1.2.1 Clinical Experience for AL-335 With or Without ODV and SMV

1.2.1.1 AL-335 Monotherapy

As of 8 September 2016, the safety and pharmacokinetics of AL-335 monotherapy versus placebo as single ascending doses (SAD) administered orally ranging from 100-1,200 mg has been evaluated in 48 healthy volunteers in Parts 1 and 2 of Study AL-335-601. Safety and pharmacokinetic (PK) differences after receiving a 400-mg tablet in the fed versus fasted state were assessed in Part 2 of this study. In both of these Parts of the study, all doses of AL-335 were well tolerated with only 3 treatment-emergent adverse events (TEAEs) being reported. All TEAEs (palpitations [N=1 event] and toothache [N=2 events in 1 subject]) occurred in AL-335-treated subjects (100 and 200 mg doses, respectively), however, none of these events were considered serious, severe in intensity, nor likely related to AL-335. No TEAEs were reported in subjects receiving single doses of AL-335 greater than 200 mg. Additionally, no clinically significant findings were observed with respect to clinical laboratory, vital signs, physical examination, Holter, or electrocardiogram (ECG) recordings.

In the multiple ascending doses part of AL-335-601 (Part 3), as of 8 September 2016, 64 subjects with CHC infection (including subjects with genotype (GT) 1, 2, 3, and 4 infection without cirrhosis and subjects with GT1 infection with compensated cirrhosis) have received 7 daily doses of up to 1200 mg of AL-335 or placebo. Among these subjects, no treatment-emergent SAEs have been reported and only 1 TEAE (acute tonsillitis, placebo group) led to study drug discontinuation. Among the TEAEs (N=26) reported in subjects dosed with AL-335, 14, 7, and 1 have been mild, moderate, or severe in intensity, respectively. The severe AE (CK elevation; peak 10× upper limit of normal [ULN]) occurred on Dosing Day 3 in a subject who received 800 mg AL-335. The subject, who is a professional athlete, had an elevated creatine kinase (CK) 1.9× ULN) at baseline and admitted to having exercised prior to the event. The subject's CK elevations were asymptomatic and declined despite continued dosing and did not require discontinuation of study drug. The most commonly reported (≥2 events) TEAEs in subjects receiving AL-335 were: headache (7 events), hyperbilirubinemia (2 events), elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) (2 events each, all of which occurred after completion of dosing in these CHC-infected subjects), drowsiness (2 events), and common cold (2 events). None of these AEs in AL-335-treated subjects occurred in a significant imbalance relative to subjects dosed with placebo, nor were any of these considered clinically significant enough to require intervention (e.g., premature discontinuation of study drug). No clinically significant ECG, laboratory, vital sign, or physical exam findings suggestive of a safety concern have been identified. No important differences in the safety profile of AL-335 were

identified between subjects infected with CHC in the presence or absence of compensated cirrhosis.

In this study, the mean maximal reduction of HCV RNA after 7 days of dosing with 400 mg of AL-335 was -2.7 log_{10} IU/mL. The mean maximal reduction of HCV RNA after 7 days of dosing with 800 mg of AL-335 in GT1, 2, and 3 groups was -4.0, -4.5 and -4.8 log_{10} IU/mL, respectively. The mean maximal reduction of HCV RNA after 7 days of dosing with 1,200 mg of AL-335 in GT1 subjects was -4.5 log_{10} IU/mL (preliminary data). In subjects with GT1 and compensated cirrhosis, the mean maximal reduction after 7 days of dosing with 800 mg AL-335 was -3.5 log_{10} IU/mL. No viral breakthrough was observed.

With respect to pharmacokinetics, in Study AL-335-601, AL-335 was rapidly (half-life <1 hour) converted to ALS-022399 and subsequently to ALS-022227. PK data from the single ascending dose phase also demonstrate that plasma exposures of AL-335 and its metabolites ALS-022399 and ALS-022227 (parent nucleoside), increased linearly up to the 800 mg dose; increases were less than dose proportional between the 800 and 1,200 mg doses, especially for ALS-022227 which reached a plateau at 1,200 mg. Upon administration of AL-335 with high fat food in Part 2 of the study, delayed time to reach the maximum plasma concentration (T_{max}) was noted for all 3 analytes. A slight increase in AL-335 and ALS-022399 area under the plasma concentration-time curve (AUC) was observed with no significant changes in maximum drug concentration (C_{max}). Food did not affect C_{max} or AUC of ALS-022227. Inter subject variability in plasma exposure for 3 analytes were reduced when AL-335 was administered with food.

In the multiple ascending dose part of Study AL-335-601, following repeated 800 mg AL-335 administrations in subjects with differing genotypes, no difference was observed in the exposure for AL-335, ALS-022399 or ALS-022227. Consistent with SAD findings, a less than dose-proportional increase in AL-335, ALS-022399 and ALS-022227 exposure was observed between 800 mg qd and 1,200 mg qd. For subjects with CHC GT1 infection with compensated cirrhosis, an increase in C_{max} and $AUC_{0\text{-last}}$ for AL-335 (~30% to 40%) and ALS-022399 (~20%) was seen compared to the CHC GT1-, 2- and 3-infected subjects without compensated cirrhosis.

1.2.1.2 AL-335 in Combination With ODV and SMV

Study AL-335-602

The safety and pharmacokinetics of multiple doses of varying combinations of AL-335, ODV, and SMV was assessed in 32 healthy volunteers in Study AL-335-602. Subjects were administered on a daily basis at least one of the following compounds: 800 mg AL-335, 150 mg SMV, and/or ODV, given as a 150 mg LD on the first day of treatment followed by a 50 mg maintenance dose on subsequent days. All subjects were dosed with study drugs for a total duration of 23 days.

Among enrolled subjects, no treatment-emergent serious adverse events (SAEs) were reported. Only 1 TEAE (tooth abscess, assessed as unrelated to study drugs) resulted in treatment discontinuation. All reported TEAEs (N=20) were mild (N=14) or moderate (N=6) in severity. The most commonly reported TEAEs (i.e., ≥2 events) were fatigue (N=8 events) and soft stools (N=3 events), none of which were considered clinically concerning or required medical

intervention (e.g., concomitant medication). No clinically significant laboratory, ECG, vital sign, or physical exam findings suggestive of a safety concern have been identified.

AL-335 had no impact on either SMV or ACH 3102 exposures. ODV increases SMV exposures by approximately 1.8-fold. SMV increases ODV exposure by 1.5-fold. Co-administration of all 3 drugs resulted in significant increase in AL-335 exposures (7- to 8-fold) and metabolite ALS-022399 (2.6- to 2.8-fold) and slight increase in ALS-022227 (1- to 1.1-fold), as well as a 1.6-fold increase in both SMV and ODV exposures.

Study HPC1001: Drug drug interaction with oral contraceptives

Effect of steady-state AL-335, ODV and 3 DAA combination (SMV+AL-335 +ODV) on single dose pharmacokinetics, safety and tolerability of oral contraceptives (drosperinone and ethinyl estradiol) was assessed in 24 healthy subjects. Preliminary results indicate that there was no effect of AL-335, ODV or 3 DAA combination on the pharmacokinetics of drosperinone. Ethinyl estradiol pharmacokinetics were not impacted by AL-335 or ODV. There was a slight increase in ethinyl estradiol exposure (Cmax 29% and AUC 19%) with the 3 DAA combination. Therefore the 3DAA combination is not considered to affect the efficacy of oral contraceptives and no dose-adjustment is required.

Study AL-335-604

As of 6 February 2017, 123 CHC subjects have received at least one dose in Cohorts 1, 1b, 2 and 3 (N=20/cohort) and in Cohorts 4 (n=13), 5 (n=19) and 6 (n=11) in Study AL-335-604. Actual dosing regimens in these cohorts and available viral kinetic (VK) data at posttreatment visits (as of 17 February 2017) are defined in Table 1-1.

Table 1-1. Completed, Initiated and Planned Cohorts^ (Cohorts 1-15), Including Available VK Data – As of 17 February 2017

Cohort #	GT	Cirrhosis	AL-335 dose (mg)	ODV dose (mg)	SMV dose (mg)	Duration (weeks)	Cohort Status	Number (%) achieving SVR
1	1	N	400	50 QD	100	8	Through SVR24	20/20 (100%), SVR24
1b	1	N	800	50 QOD	--	8	Through SVR24	18/20 (90%), SVR24
2	1	N	800	50 QOD	75	8	Through SVR24	20/20 (100%), SVR24
3	1	N	800	50 QOD	75	6	Through SVR24	20/20 (100%), SVR24
4	1	N	800	50 QOD	--	8 (N=5) 12 (N=8)	Through SVR24 Through SVR12	3/5 (60%), SVR24 7/8 (88%), SVR12
5	3	N	800	50 QOD	75	8 (N=5) 12 (N=14)	Through SVR24 Through EOT	0/5 (0%), SVR24 13/14 (93%), EOT
6	1	Y	800	50 QOD	75	8	Enrolling (N=11)	9/10 (90%), SVR12*
7	1	Y	800	25 QD	75	8	Screening/Planned	N/A
8	1	Y	800	25 QD	75	8	Screening/Planned	N/A
9	1	Y	800	25 QD	75	12	Screening/Planned	N/A
10	1	Y	800	25 QD	75	12	Screening/Planned	N/A
11	2	Y	800	25 QD	75	12	Screening/Planned	N/A
12	2	Y	800	25 QD	75	8	Screening/Planned	N/A
12-15	TBD							

* Subject 11 has completed treatment. SVR visit results pending.

^ N=10-20 per cohort; In any ongoing cohorts in which a dosing regimen is modified (e.g., treatment duration is extended) due to apparently insufficient efficacy/safety, the cohort size may be increased such that 20 subjects at the final dosing regimen are enrolled in that cohort. TBD: to be determined

In this study, two treatment-emergent SAEs were reported. One event, which occurred in Cohort 1b, was transition cell carcinoma of the urethra, which was identified during the trial when the subject reported a history of recurrent urinary tract infections and macroscopic hematuria, both of which began prior to enrollment in the study. This event was considered unrelated to study drug. A second event, Mobitz Type I 2nd degree AV block, occurred in a subject in Cohort 1 with a mean PR of 204 msec at baseline that then became progressively longer. After 5 weeks of daily dosing with 400 mg AL-335, 50 mg ODV, and 100 mg SMV, she developed Wenckebach phenomenon. The subject had no cardiac history, and was not taking any systemic concomitant medications. The Investigator indicated that she was asymptomatic during the course of this event. A cardiac evaluation, including clinical assessment by a cardiologist, CK assessments, and echocardiograms (at baseline, after 4 weeks' dosing, at time of study drug discontinuation, and 4 weeks after discontinuing study drug) were all unremarkable. This PR prolongation/Wenckebach event was considered probably attributable to ODV (events similar to this have been reported in other studies of ODV), but was also considered possibly related to SMV and AL-335. Due to the progressive nature of the subject's PR prolongation and the need for combination therapy to minimize emergence of viral resistance, all 3 study drugs were discontinued in this subject at Week 5. After discontinuing study drugs, the subject's Wenckebach/progressive PR prolongation resolved with a return to her baseline PR interval. A second subject had a baseline elevated PR interval (~240 msec) which did not change significantly in the presence of dosing, however, in light of the SAE described above, as a

precaution, ODV was discontinued in this subject. These are the only 2 subjects that have prematurely discontinued study drug.

As of 6 February 2017, a total of 336 TEAEs have been reported in Study AL-335-604, all of which were mild (N=306) or moderate (N=30) in severity. The most commonly reported (≥6 events) events were: contusion, cough, diarrhea, fatigue, headache, back pain, and upper respiratory tract infection. Among the subset of subjects with cirrhosis that have received at least one dose of study drugs (N=11), study treatment has been well tolerated with 48 TEAEs reported: all of which were mild (N=43) or moderate (N=5). There were no commonly reported events (≥6 events) at the time of this protocol amendment. With the exception of the single observed case of progressive PR prolongation with resulting Wenckebach phenomenon described above, no clinically significant echocardiogram, ECG, laboratory, vital sign, or physical exam findings suggestive of a safety concern have been identified. Additionally, no important differences in the safety profile of AL-335 have been identified between subjects infected with CHC in the presence or absence of compensated cirrhosis.

With respect to efficacy, a description of available SVR data in ongoing Study AL-335-604 is presented in Table 1-1.

In Cohorts 1b and 4, both evaluating the combination of AL-335 and ODV without SMV (2DAA) for 8 weeks in non-cirrhotic treatment-naïve genotype 1 HCV-infected subjects, 4 subjects, (N=2 in Cohort 1b, N=2 in Cohort 4) have experienced virologic relapse to date. In the 2 relapse subjects from Cohort 1b, sequencing has identified the emergence of mutations in the HCV NS5A gene known to confer resistance to ODV (M28T in combination with T64A in Subject [redacted] and Y93H in combination with T21A in Subject [redacted]) but no emerging mutations in the HCV NS5B gene associated with AL-335 resistance were observed. Sequencing data are not yet available for the relapse subjects in Cohort 4. Based on the first 3 cases of virologic relapse in 2DAA-containing regimens, a decision was made to stop further enrollment in Cohort 4, in which 13 subjects had been enrolled. At the time this decision was made, 8 subjects in Cohort 4 were still on treatment and, in an effort to minimize further cases of virologic relapse in these subjects receiving 2DAA, the treatment duration was extended from 8 to 12 weeks. The subjects in Cohort 4 who had already completed treatment by the time this decision was made continue to be closely monitored. In Cohort 5, which is still ongoing, the duration of treatment was increased from 8 to 12 weeks in response to initial antiviral data suggesting that longer treatment might be more appropriate for this population.

Preliminary data from the PK substudy up to Cohort 6 (as of 17 February 2017) are provided in Table 1-2. Increasing the dose of AL-335 from 400 mg (Cohort 1) to 800 mg in patients without cirrhosis (Cohorts 1b to 4) increased AL-335 and its metabolites (ALS-022399, monophosphate precursor, and ALS-022227, parent nucleoside) exposures in a less than dose-proportional manner. The exposures of the parent nucleoside metabolite ALS-022227 at the 800-mg dose in this study were similar to those previously observed at the 800-mg dose level in study AL-335-601, , at which AL-335 demonstrated potent viral activity over a 7 day period. There was no apparent difference in AL-335 and its metabolites' exposures in patients with compensated cirrhosis (Cohort 6), although limited PK data are currently available. (n=5) . ODV exposure in Cohort 1 (mean C_{max} and C_{24h} were 636 and 384 ng/mL, respectively) was ~2- to 2.5-fold higher than observed in previous studies in which ODV was found to be highly efficacious

(Study ACH102-017: mean C_{max} and C_{trough} were 182 and 119 ng/mL, respectively, in Group 1 and 215 and 133 ng/mL, respectively, in Group 2). ODV exposures decreased in proportion to the change in dosing administration (from qd in Cohort 1 to qod in Cohorts 1b, 2, and 3). Available PK data from Cohort 6 (N=6), indicated that the observed range of ODV exposures were similar in compensated cirrhotic patients (Cohort 6) compared to non-cirrhotic patients on the same dosing regimen (Cohorts 2 and 3). A less than dose-proportional decrease in SMV exposure levels was observed when decreasing the dose of SMV from 100 mg (Cohort 1) to 75 mg (Cohorts 2 and 3). Exposures at the SMV 75-mg dose were generally consistent with those previously found to be efficacious (TMC435-C205). SMV exposures were similar in compensated cirrhotic patients (Cohort 6) compared to non-cirrhotic patients on the same dosing regimen (Cohorts 2 and 3).

Table 1-2. Preliminary Mean (SD)* PK Parameters of AL-335 and its Metabolites (ALS-022399 and ALS-022227), ODV, and SMV at Week 2 up to Cohort 6 (AL-335-604 PK Substudies)

Cohort	Dosing Regimen	Analytes	C_{max} (ng/mL)	AUC_{0-24h} (ng•h/mL)	T_{max} (h)
1 (N=11)	AL-335 400 mg qd+ODV 50 mg qd +SMV 100 mg qd	ALS-022335	415 (318)	1,043 (895)	2 (0.5-4)
		ALS-022399	104 (52)	467 (224)	3 (1-6)
		ALS-022227	364 (129)	2,916 (1,028)	4 (2-4)
		SMV	1,928 (1,205)	25,025 (15,228)	6 (4-12)
		ODV	636 (261)	11,809 (4,918)	6 (4-12)
1b (N=8)	AL-335 800 mg qd+ODV 50 mg qod for 8 weeks	ALS-022335	533 (256)	1,166 (552)	3 (1-4)
		ALS-022399	139 (53)	606 (212)	3 (2-4)
		ALS-022227	355 (144)	2,910 (824)	4 (3-6)
		SMV	NA	NA	NA
		ODV	344 (177)	5,407 (2,965)	6 (4-12)
2 (N=3)	AL-335 800 mg qd+ODV 50 mg qod +SMV 75 mg qd for 8 weeks	ALS-022335	734 (863)	2,062 (2,851)	2 (1-4)
		ALS-022399	184 (147)	1,088 (963)	3 (2-4)
		ALS-022227	644 (227)	5,417 (1,922)	4 (3-6)
		SMV	1,031 (815)	14,415 (12,274)	6 (6-6)
		ODV	259 (184)	4,416 (2,945)	9 (9-9)
3 (N=6)	AL-335 800 mg qd+ODV 50 mg qod +SMV 75 mg qd for 6 weeks	ALS-022335	631 (370)	1,499 (920)	1 (1-2)
		ALS-022399	180 (73)	864 (375)	3 (2-3)
		ALS-022227	641 (113)	5,026 (1,436)	3 (2-4)
		SMV	1,566 (1,160)	22,681 (20,159)	6 (4-9)
		ODV	425 (104)	7,087 (2,132)	6 (6-9)
4 (N=1)	AL-335 800 mg qd+ODV 50 mg qod for 8 or 12 weeks	ALS-022335	674	1753	3
		ALS-022399	176	932	4
		ALS-022227	554	5155	6
		SMV	NA	NA	NA
		ODV	148	1939	6
5 (N=0)	AL-335 800 mg qd+ODV 50 mg qod +SMV 75 mg qd for 8 or 12 weeks	ALS-022335	ND	ND	ND
		ALS-022399	ND	ND	ND
		ALS-022227	ND	ND	ND
		SMV	ND	ND	ND
		ODV	ND	ND	ND
6 (N=5)	AL-335 800 mg qd+ODV 50 mg qod +SMV 75 mg qd for 8 weeks in patients with compensated cirrhosis	ALS-022335	561 (283)	1131 (652)	1 (1-1)
		ALS-022399	159 (63)	655 (213)	2 (1-3)
		ALS-022227	633 (355)	4756 (1867)	3 (2-6)
		SMV	1853 (959)	27677 (16008)	6 (4-6)
		ODV	248 (206)	4215 (3018)	6 (3-9)

*T_{max}: median (range)
NA = not applicable; ND = no data

Additional information regarding AL-335 is available in the AL-335 Investigator's Brochure and Addendum.

1.3 ODV Background

ODV is a nonstructural protein 5A (NS5A) inhibitor being developed as an orally administered anti-HCV therapeutic. ODV has demonstrated potent antiviral activity against all genotypes, including HCV replicons that show resistance to other HCV NS5A inhibitors.

ODV has demonstrated a low inhibition potential for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5. ODV is primarily cleared by biliary secretion, is not significantly metabolized, and is not expected to be involved with clinically significant drug-drug interactions associated with the CYP450 enzyme system. ACH is not a substrate or inhibitor of transporters such as MDR1 (P-gp), OATP1B1/1B3, OAT1/3, OCT2, BCRP, MRP2, MRP3, and BSEP.

No clinically significant drug-drug interaction was observed between ODV and sovaprevir, montelukast, atazanavir/ritonavir, efavirenz/emtricitabine/tenofovir disoproxil fumarate, darunavir/ritonavir, or raltegravir.

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

1.3.1 Summary of Cardiac Safety in Animal Studies

In vivo, no cardiac effects occurred at exposure levels (Cmax and AUC) about 6 times the target clinical exposure of ODV (when administered at a dose of 25 mg qd in combination with SMV 75 mg qd and AL-335 800 mg qd). After repeated dosing of ODV in rats and dogs with exposure levels (C_{max} and AUC) 14 times the target clinical exposure, increased heart weights were noted. In repeated dose studies in the dog, administration of ODV, at similar exposure levels, was associated with ECG changes (prolonged PR intervals and/or 1st degree AV block, prolonged QRS and QT intervals) and decreased heart rate. Echocardiography was performed in the 26-week toxicity study in the dog and revealed progressive left ventricular dilatation, eccentric hypertrophy and minor reduction in ejection fraction (the latter within normal reference range) associated with increased stroke volume while the cardiac index was not affected.

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

For more information refer to the Investigator's Brochure and its addendum.

Evaluation of the results from an additional 8-week repeat dose (70 mg/kg orally) mechanistic study in the telemetered dog is currently ongoing. In this study, ODV was administered at a dose corresponding to approximately 200 times a 25-mg dose in humans. Preliminary data showed a

decrease in cardiac contractility, resulting in a decrease in ejection fraction and systolic and diastolic blood pressure.

The increase of PR/PQ interval preceded an increase in ventricular mass. QT interval increased later in the study. Information of exposure levels achieved with this dose, biomarker data and histopathology are pending. The clinical relevance of these findings is not yet completely understood. Importantly, analysis of all available echocardiography assessments from clinical studies in humans has not shown safety signals to date (see below).

1.3.2 Previous Clinical Experience for ODV

In clinical studies of ODV, including administration of single 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 (LD) on Day 1, but ODV has been used successfully without a LD in a recent Phase 2a study, ACH102-017.

Odalasvir has been studied in combination with other anti-viral agents such as RBV, sovaprevir, and sofosbuvir, and has been well-tolerated in each of these settings. Specifically, after single (Studies ACH102-001, ACH102-003, ACH102-010, ACH102-015, ACH102-020) and multiple dosing (Studies ACH102-001, ACH102-008, ACH102-009, ACH102-011, ACH102-012, ACH102-013 and ACH786-001) of ODV in healthy volunteers and single (Study ACH102-002) and multiple dose studies in HCV-infected subjects (Studies ACH102-005 and ACH102-007), no dose-related trends in treatment-emergent AEs were observed. In placebo-controlled studies in healthy volunteers, no differences in the frequency of treatment-emergent AEs (preferred terms) were observed between the active treatment and the placebo group. In a placebo-controlled study in chronic hepatitis C (CHC)-infected subjects (Study ACH102-007), headache, nausea, bilirubin increases, and anemia were safety findings that occurred more frequently in subjects treated with ODV (150 mg LD followed by 50 mg qd)+sovaprevir (200 or 400 mg qd) + RBV (1,000 or 1,200 mg/day; twice daily [bid] regimen) treatment compared to placebo-treated subjects. However, these are known to occur with RBV administration and none led to permanent treatment discontinuation. RBV dosing was interrupted or the dose was reduced in 5 (6.6%) subjects on active treatment.

Overall, in the approximately 440 ODV-treated subjects with data available as of 21 March 2016, the majority of treatment-emergent AEs were Grade 1 or 2 in severity. No Grade 4 treatment-emergent AEs have been reported. Five Grade 3 treatment-emergent AEs were reported in 4 subjects. One healthy volunteer (Study ACH102-009) experienced a Grade 3 asymptomatic elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT; 519 and 518 U/L, respectively), which were considered probably related to ODV, and led to study drug discontinuation. Another healthy volunteer (Study ACH102-001) experienced a Grade 3 elevation of creatine phosphokinase (7,729 U/L), which was considered unrelated to ODV. A Grade 3 worsening of anemia and Grade 3 Wenckebach phenomenon was reported in Study ACH102-005 in subjects with CHC. Both events were considered unrelated to ODV by the investigator and did not lead to study drug discontinuation. Except for the above mentioned subject in Study ACH102-009, no subjects discontinued ODV treatment due to an AE in any of the studies.

Overall, SAEs were reported in 3 subjects that were dosed with ODV in studies outside of the current study. One healthy volunteer, who received a single 600 mg dose of ODV during Study ACH102-001 developed a gastroenteritis, which was considered unrelated to ODV, requiring hospitalization. One subject with CHC who had received ODV (150 mg LD; 50 mg maintenance dose) + sovaprevir (400 mg) + RBV (weight-based 1,000 or 1,200 mg dose) in Study ACH102-007 experienced chest pain on Day 15. The subject was hospitalized for cardiac evaluation, which was negative. A third subject experienced an SAE of intervertebral disc protrusion that occurred more than 28 days after the end of treatment (EOT) visit in Study ACH102-017, and was considered unrelated to ODV and sofosbuvir.

Cardiac Safety

In the placebo-controlled studies ACH102-001, ACH102-002 and ACH786-001 in healthy volunteers and ACH102-007 in CHC-infected subjects, no notable trends in mean cardiac intervals and durations over time as compared with placebo were noted for ODV dosing groups. However, in the multiple-dose, placebo-controlled portion of Study ACH102-001, in healthy volunteers, PR categorical outliers were noted only in higher dose ODV groups. A total of 4 of 32 (12.5%) subjects who received ODV had treatment-emergent PR values >200 msec, as compared with none of the eight subjects that received placebo. When ODV was co-administered with deldeprevir (also known as ACH-0142684), an investigational HCV protease inhibitor, in Study ACH786-001, a higher number of subjects with PR >200 msec was noted in the active treatment groups (N=7; 2 subjects during ACH-0142684 monotherapy, 2 subjects during ODV monotherapy, and 3 subjects during ACH-0142684 + ODV treatment) as compared with placebo(N=0).

Electrocardiogram cardiac monitoring in Phase 1b/2a studies ACH102-005 and ACH102-007 in HCV-infected subjects did not identify any clinically significant trends in ECG parameters. In contrast to the placebo-controlled studies in healthy volunteers, no trends in PR categories or other ECG findings were noted with weekly ECG monitoring in the placebo-controlled, 12-week sovaprevir/RBV co-administration study (ACH102-007) in CHC-infected subjects. Cardiac monitoring in Study ACH102-005 in HCV-infected subjects did not identify any clinically significant trends in ECG parameters. In Study ACH102-005 one treatment-emergent PR prolongation was observed; by Week 12 this event had evolved to a transient type 1 second-degree AV block (Wenckebach). The cardiologist assessed the subject's second-degree AV block to be of undetermined etiology but unlikely due to study drug. The subject completed the full course of 12 weeks therapy with ODV and RBV.

Echocardiograms were performed in Study ACH102-007. There were no clinically significant echocardiogram findings and no treatment-related trends in echocardiographic parameters.

Efficacy

A summary of antiviral effect and efficacy data of ODV from clinical studies with ODV as monotherapy and ODV in combination with DAAs other than AL-335±SMV is provided below.

In **Study ACH102-002**, 18 subjects with GT HCV infection were administered single doses of ODV, and the mean (range) maximal HCV RNA decrease from baseline (log_{10} IU/mL), was 4.04 (3.32 to 4.62) in the 25 mg dose group, 3.78 (3.35 to 4.16) in the 50 mg dose group, 3.52 (2.91 to 3.98) in the 150 mg dose group, and 3.93 (3.40 to 4.60) in the 300 mg dose group.

In **Study ACH102-005**, 8 subjects with GT1b HCV infection and interleukin 28B (*IL28B*) genotype CC were administered ODV as 225 mg LD followed by 75 mg qd and weight-based RBV (1,000 or 1,200 mg daily) for 12 weeks. Six out of 8 subjects had a rapid decline in HCV RNA with HCV RNA <lower limit of quantification (LLOQ) by Week 3, with maintenance of viral suppression through the EOT at Week 12. Of these 6 subjects, 5 achieved SVR 4 weeks after planned EOT (SVR4), 4 achieved SVR 12 weeks after planned EOT (SVR12), and 3 achieved SVR 24 weeks after planned EOT (SVR24). The remaining 2 subjects had a slower but continuous decline in HCV RNA over the 12-week treatment period with HCV RNA >LLOQ at EOT. There were no instances of on-treatment viral breakthrough in this study.

Study ACH102-007 was a study in treatment-naïve subjects with GT1 HCV infection (8 GT1b and 12 GT1a-infected subjects) who received ODV (150 mg LD on Day 1 followed by a 50 mg qd dose) in combination with weight-based RBV, and sovaprevir (200 mg in Group 1; 400 mg in Group 2) for 12 weeks. For both Group 1 and Group 2, administration of sovaprevir, ODV and RBV resulted in a rapid virologic response with HCV RNA <LLOQ by Week 1-2 in all active subjects who received at least 2 weeks of study drugs, while placebo subjects had little or no change in HCV RNA. Of the 12 GT1a-infected subjects overall, 7 subjects (58.3%) had undetectable HCV RNA by Week 4 (rapid virologic response [RVR]). Seven GT1a-infected subjects experienced virologic failure with viral breakthrough in 6 subjects and relapse in 1 subject. In addition, 1 subject withdrew consent at Week 1 (personal reasons) resulting in a SVR4, SVR12 and SVR24 of 33% in HCV GT1a-infected subjects. Of the 8 GT1b-infected subjects, all subjects (100%) had undetectable HCV RNA at Week 4 and at Week 12 and achieved SVR4, SVR12 and SVR24.

Study ACH102-017 was a Phase 2, open-label, randomized, controlled, partial crossover study to evaluate the efficacy, safety, and tolerability of 8 weeks (Group 1) or 6 weeks (Group 2 and Group 3) of ODV (50 mg qd; fasted; without LD) and SOF (400 mg qd) in treatment-naïve subjects with GT1 HCV infection. All subjects (N=30) on active treatment in Group 1 (8-week treatment) Group 2 and Group 3 (6-week treatment) achieved SVR12 and SVR24, i.e., 12 subjects achieved SVR24 after 8 weeks of treatment with SOF and ODV and 18 subjects achieved SVR24 after 6 weeks of treatment with SOF and ODV. The efficacy data suggest the adequacy of the 6-week regimen with the combination of ODV and SOF.

A complete summary of the clinical characteristics of ACH-0143102 and clinical data obtained with regimens not including AL-335 co-administration can be found in the Investigator's Brochure and Addenda.

1.4 SMV Background

SMV is an orally active, small molecule inhibitor of the NS3/4A protease of HCV and indicated for the treatment of GT1 and GT4 chronic HCV infection, including subjects with Child Pugh A cirrhosis, as a component of a combination antiviral treatment regimen. SMV is available as a hard capsule for oral administration. The recommended dose is one 150 mg capsule taken qd with food. Each capsule contains 154.4 mg of SMV sodium salt, which is equivalent to 150 mg of SMV. The capsules contain the following inactive ingredients: colloidal anhydrous silica, croscarmellose sodium, lactose monohydrate, magnesium stearate, and sodium lauryl sulphate.

SMV is highly protein-bound in plasma (>99.9%) at pharmacologically relevant concentrations. The blood:plasma ratio of SMV is approximately 0.66, indicating that SMV is largely contained in the plasma rather than the cellular components of the blood.

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

In CHC GT1-infected subjects, the exposure was generally greater than observed in healthy subjects. In subjects with CHC, the terminal elimination half-life 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.

A number of Phase 1 PK and drug-drug interaction studies have been conducted with SMV and are summarized in the Investigator's Brochure including the following: the SMV-methadone interaction study (C110) that demonstrated no interaction between SMV and methadone and the thorough QT interval corrected for heart rate (QTc) study (Study C117) that demonstrated no effect of SMV upon the QT interval in humans.

Cytochrome P450 (CYP) 3A enzymes are mainly involved in the metabolism of SMV, so plasma concentration will significantly increase if taken with medications that are strong CYP3A4 inhibitors (e.g., macrolides, azole antifungal agents, ritonavir) and will significantly decrease if taken with strong CYP3A4 inducers (e.g., efavirenz, rifampicin). Hepatic uptake of SMV is mediated by OATP1B1, inhibitors of this transporter may increase plasma concentrations of SMV (e.g., cyclosporine).

SMV is a mild inhibitor of intestinal (but not hepatic) CYP3A activity and a mild inhibitor of CYP1A2, which is only relevant for drugs solely metabolized by these enzymes, and having a narrow therapeutic index (e.g., certain anti-arrhythmics). In addition, drug-drug interaction studies with transporter substrates suggest that SMV is a mild inhibitor of P-gp and a moderate inhibitor of organic anion-transporting polypeptide (OATP)1B1 in vivo. Thus, co-administering SMV with medications that are substrates for P-gp or OATP (such as statins) may lead to increased plasma concentrations of these medications.

SMV is primarily metabolized by the liver. Compared to HCV-uninfected subjects with normal hepatic function, the mean steady-state AUC of SMV was 2.4-fold higher in HCV-uninfected subjects with moderate hepatic impairment (Child-Pugh Class B) and 5.2-fold higher in HCV-uninfected subjects with severe hepatic impairment (Child-Pugh Class C). No dose adjustment of SMV is necessary in patients with mild hepatic impairment (Child-Pugh Class A).

1.4.1 Previous Clinical Experience for SMV

Efficacy

For approval, SMV was investigated in three Phase 3 studies involving 1,178 patients with HCV of GT1. The first 2 studies included treatment-naïve patients, while the third included patients who relapsed following treatment with interferon-based therapy. All 3 studies compared SMV with placebo when taken in combination with pegylated interferon alfa (PegIFN) and RBV.

The combined results of the first 2 studies demonstrated that around 80% (419 out of 521) of patients taking SMV achieved HCV RNA levels <LLOQ by 12 weeks after the end of treatment, compared with 50% (132 out of 264) of patients on placebo. In the third study, around 80% (206 out of 260) of patients taking SMV achieved HCV RNA levels <LLOQ by 12 weeks after the end of treatment, compared with around 37% (49 out of 133) of patients on placebo. An analysis of these studies showed that SMV was less effective in a subgroup of patients infected with HCV GT1a who harbor an NS3 Q80K polymorphism at baseline. Additional studies involving patients with HCV of GT4 and patients with HIV co-infection showed results consistent with those in patients with GT1.

SMV taken together with sofosbuvir has been investigated in the Phase 2 study TMC435HPC2002 (COSMOS) which evaluated the efficacy and safety of 12 or 24 weeks of SMV 150 mg qd in combination with sofosbuvir 400 mg qd, with and without RBV, in HCV GT1-infected subjects with METAVIR F0-F2 who were prior null responders to PegIFN/RBV therapy (Cohort 1, N=80) and subjects with METAVIR F3-F4 who were prior null responders to PegIFN/RBV therapy or treatment-naïve (Cohort 2, N=87). The results of this study demonstrated SVR12 rates of ≥90%, irrespective of treatment duration (12 or 24 weeks), use of RBV or treatment history (prior null responders to the combination of PegIFN and RBV or treatment-naïve)

In the Phase 2a study C202, treatment-naïve subjects with HCV genotypes 2, 3, 4, 5, and 6 infection were treated with SMV 200 mg qd monotherapy for 7 days. Monotherapy with oral SMV 200 mg qd for 7 days showed potent antiviral activity against HCV GT2, 4, 5, and 6. For the primary endpoint at Day 8, the mean (±standard error [SE]) change in plasma HCV RNA (log_{10} IU/mL) from baseline was the greatest for genotypes 6 (-4.35±0.29) and 4 (-3.52±0.43), followed by genotypes 2 (-2.73±0.71) and 5 (-2.19±0.39). No clear antiviral activity with SMV monotherapy was observed against HCV GT3. The efficacy in HCV GT4-infected subjects was confirmed in the Phase 3 study HPC3011.

SMV at a dose of 100 mg qd in combination with PegIFN/RBV has demonstrated good efficacy and a favorable safety/tolerability profile in Japanese HCV GT1 treatment-naïve and treatment-experienced subjects and the exposure at this dose was similar to the exposure of 150 mg qd in Caucasian subjects.

In HCV GT1b treatment-naïve subjects from China and South Korea, SMV 100 mg and 150 mg were found equally efficacious, with efficacy data in line with efficacy data previously obtained in mainly Caucasian treatment-naïve HCV GT1b-infected subjects dosed with SMV 150 mg qd.

Safety

The most common AEs reported in the Phase 3 trial of SMV with PegIFN and RBV (occurring with at least 3% higher frequency compared to placebo) during the first 12 weeks of treatment included: rash (including photosensitivity), pruritus, nausea, myalgia, and dyspnea. Most of the rash events were of mild or moderate severity (Grade 1 or Grade 2). Severe (Grade 3) rash occurred in 1% of SMV-treated subjects and there were no reports of life-threatening (Grade 4) rash. Discontinuation of SMV or placebo due to rash occurred in 1% of SMV-treated subjects, compared to less than 1% of placebo-treated subjects. The frequencies of rash and photosensitivity reactions were higher in subjects with higher SMV exposures. Most

photosensitivity reactions were of mild or moderate severity (Grade 1 or 2). Two SMV-treated subjects experienced photosensitivity reactions which resulted in hospitalization. No life-threatening photosensitivity reactions were reported.

All dyspnea events reported were of mild or moderate severity (Grade 1 or 2), there were no Grade 3 or 4 dyspnea events reported and no subjects discontinued treatment due to dyspnea. Sixty-one percent (61%) of dyspnea events occurred in the first 4 weeks of treatment with SMV.

The only difference between treatment groups for laboratory parameters was an elevation in bilirubin. Elevations in bilirubin were predominately mild to moderate (Grades 1 or 2) in severity, and included elevation of both direct and indirect bilirubin. Elevations in bilirubin occurred early after treatment initiation, and normalized upon cessation of SMV. Bilirubin elevations were generally not associated with elevations in liver transaminases. Consult the investigator brochure for SMV for further information.

Clinical Pharmacology
SMV is orally bioavailable and C_{max} is typically achieved between 4 to 6 hours post dose. Steady-state is reached after 7 days of daily treatment with 150 mg of SMV. Plasma exposure of SMV in HCV-infected subjects is about 2- to 3-fold higher compared with that observed in HCV-uninfected subjects.

SMV is highly protein-bound in plasma (>99.9%) at pharmacologically relevant concentrations. The blood:plasma ratio of SMV is approximately 0.66, indicating that SMV is largely contained in the plasma rather than the cellular components of the blood.

Administration of SMV with food to healthy subjects increased the relative bioavailability by 61% and 69% after a high-fat, high-caloric (928 kcal) and normal-caloric (533 kcal) breakfast, respectively, and delayed the absorption by 1 hour and 1.5 hours, respectively (Janssen Therapeutics 2016).

1.5 Rationale for the Study and Study Design

AL-335 is a nucleotide analog being developed for the treatment of HCV. Data from several clinical trials have demonstrated the potential for the effective combination of nucleotide analogs with NS5A or NS3 inhibitors for the treatment of chronic HCV infection (Lawitz et al. 2014). This study is designed to determine the initial safety and efficacy of concomitant administration of ODV (NS5A inhibitor), AL-335 (nucleotide analog inhibitor), ±SMV (NS3 protease inhibitor), over a 4- to 12-week treatment period in treatment-naïve and treatment experienced subjects with CHC. The results of this study will assist in determining the design of subsequent studies.

1.6 Rationale for Permitting Women of Child Bearing Potential

The embryo-fetal developmental studies conducted with AL-335 and ODV in rats and rabbits do not indicate significant risk to a fetus when given to animals over critical period of organogenesis. Exposure multiples 1.8-fold (rat) to 5-fold (rabbit) of the major analyte ALS-022227 were obtained in these studies compared with human exposure at 800 mg AL-335. For ODV, 0.5-fold (rabbit) to 21-fold (rat) multiples of the exposure were obtained in these

studies as compared with the human exposure of 50 mg qod ODV (see Investigator's Brochure for details). In addition, AL-335 did not have any adverse effects/disturbances in the reproductive process from pre-mating to conception and from conception to implantation in rats up to the highest dose of 1000 mg/kg/day (2-fold above human exposures). SMV is a marketed product with Pregnancy C category (see Package Insert). Therefore, highly effective contraception in heterosexually active subjects and/or their partners is sufficient to protect subjects of child bearing potential.

1.7 Risk-Benefit Assessment

In vitro and in vivo studies, including available data from Cohorts 1-3 in this study, indicate that the planned combinations of AL-335 and ODV±SMV have the potential to successfully treat HCV infection in the populations being studied in this trial. In subjects with GT1 and 2 infection, all 3 study drugs have demonstrated significant antiviral activity in vitro/in vivo and at least in vitro, respectively. In GT3 subjects, SMV is not expected to have any direct antiviral activity; however, its boosting effects on AL-335/metabolites and ODV exposures may enhance the antiviral activity of AL-335 and ODV. Furthermore, in the event unacceptable levels of treatment failures were to occur for a given regimen or population (see Section 4.8.1), this protocol is designed to detect these failures early and discontinue further evaluation of potentially inadequate regimens. Finally, any subject that does experience treatment failure will be further characterized (i.e., viral RNA will be sequenced) and, based on this analysis, enrolled in a retreatment protocol or provided an appropriate standard of care antiviral therapy.

With respect to safety, available data to date in 121 subjects who received at least one dose of study drugs, suggest that these treatment regimens are generally well tolerated as determined by adverse events, laboratories, ECGs, echocardiograms, physical examination, and vital signs. Additionally, precautions to avoid and detect early any toxicities potentially associated with individual study drugs (e.g., cardiac toxicity with ODV, photosensitive rash and drug-drug interactions with SMV) are extensively incorporated into the protocol, thereby minimizing risk to subjects. Examples of these precautions include:

- Continuous AE assessments
- At least biweekly safety labs (through completion of dosing then at SVR4 visit)
- Weekly ECGs (through completion of dosing then at SVR4 visit)
- Monthly echocardiograms (through completion of dosing then at SVR4 visit)
- Weekly physical examinations and vital signs (through completion of dosing then at SVR4 visit)
- Education on sun avoidance and skin protection
- Extensive list of prohibited medications to minimize DDI potential

In summary, the proposed combinations of study treatments in planned patient populations can be supported on the basis of the following points:

- High SVR rates observed in the relevant cohorts evaluated to date
- An acceptable safety profile to date
- The incorporation of intensive surveillance measures to detect early futility and to be able to modify or discontinue treatment regimens associated with any
- Unacceptable treatment failures
- Emerging safety signals

2.0 STUDY DESIGN

2.1 Summary

This open-label study will assess the safety, pharmacokinetics and efficacy of the orally administered combination of AL-335 and ODV, with or without SMV in treatment-naïve and treatment experienced subjects with CHC infection. Up to 320 subjects with CHC GT1 or 2 or 3 infection will be enrolled to receive up to 1,200 mg qd of AL-335 in combination with ODV up to 50 mg qd or qod, with or without up to150 mg qd SMV.

Based on emerging safety, PK, and efficacy data, the following study parameters may be changed for ongoing and future cohorts after obtaining agreement from the Sponsor and the Principal Investigator:

- Treatment duration: 4-12 weeks
- Dose levels:
  - AL-335: 400-1,200 mg
  - ODV: 25-50 mg (dosed either qd or qod)
  - SMV: 75-150 mg (if evaluated in a cohort)
- Genotype: GT1 and/or GT2 and/or GT3; Cohorts may also be limited to specific subtypes (e.g., GT1a only) or may include all subtypes
- Cohort size: 10-20 subjects. In any ongoing cohort in which a dosing regimen is modified (e.g. treatment duration is extended) due to apparently insufficient efficacy/safety, the cohort size may be increased such that 20 subjects at the final dosing regimen are enrolled in that cohort.
- Population: Treatment-naïve non-cirrhotic HCV-infected subjects and treatment naïve or treatment experienced HCV-infected subjects with compensated cirrhosis (decompensated cirrhosis prohibited)
- Viral load: A viral load threshold may be included in determining eligibility for a cohort if higher viral loads are projected to have unacceptable efficacy. This threshold may be derived from emerging data (e.g. prior cohorts), medical literature, etc.

- Number of cohorts: Up to 16 cohorts (maximum N=320 subjects) with the above defined constraints may be enrolled.

The planned study design is depicted in the study schema in Section 2.2.

The initial 8-week treatment cohort (Cohort 1) will consist of at least 50% HCV GT1a. After 4 weeks of treatment in the 8 week treatment cohort, safety and viral load from at least 16 of 20 subjects and available PK data will be reviewed by the Sponsor in consultation with the Principal Investigator prior to initiation of enrollment of additional cohorts. If necessary, the review may be extended to include the full PK data set from the Week 2 intensive PK assessment.

After the initial cohort (Cohort 1), subsequent cohorts may be enrolled concurrently or in a staggered fashion. Effective as of approval of protocol version 7, prior to evaluating a given treatment regimen in subjects with cirrhosis or for a shorter duration, efficacy, safety, and available PK data for that treatment regimen in subjects without cirrhosis and/or for a longer duration will be reviewed. Specifically, data from at least 10 subjects at the SVR4 time point will be reviewed and, if acceptable (see Section 4.8), subsequent cohorts evaluating shorter durations and/or subjects with cirrhosis will be initiated. The timing of initiating enrollment in these subsequent cohorts will be coordinated such that SVR12 data from at least 10 subjects in the earlier cohort will be available before the end of treatment visit occurs for the first subject in the subsequent cohort. This timing is designed to enable extension of the treatment duration in the subsequent cohort if the earlier cohort is determined to have insufficient efficacy.

Based on data available as of 17 February 2017, the following cohorts have been completed, initiated or are planned (Table 2-1). Available VK data are also included. Safety, viral load and PK data from dosing regimens in subjects without cirrhosis and/or dosed for longer treatment durations will be evaluated and, if they indicate an adequate safety and efficacy profile, dosing with the same regimen in cohorts with cirrhosis or for shorter treatment durations will be permitted. Cohorts 6 through 12 are currently open for enrollment or planned at the time of this protocol finalization. The cohort regimens will only change if emerging data requires they be altered for safety purposes. Some planned cohorts may not be enrolled if emerging data are not supportive or suggest the cohort is not necessary to achieve the study's objectives.

Table 2-1. Completed, Initiated, and Planned Cohorts^ with Available VK Data

Cohort #	GT	Cirrhosis	AL-335 dose (mg)	ODV dose (mg)	SMV dose (mg)	Duration (weeks)	Cohort Status	Number (%) achieving SVR
1	1	N	400	50 QD	100	8	Through SVR24	20/20 (100%), SVR24
1b	1	N	800	50 QOD	--	8	Through SVR24	18/20 (90%), SVR24
2	1	N	800	50 QOD	75	8	Through SVR24	20/20 (100%), SVR24
3	1	N	800	50 QOD	75	6	Through SVR24	20/20 (100%), SVR24
4	1	N	800	50 QOD	--	8 (N=5) 12 (N=8)	Through SVR24 Through SVR12	3/5 (60%), SVR24 7/8 (88%), SVR12
5	3	N	800	50 QOD	75	8 (N=5) 12 (N=14)	Through SVR24 Through EOT	0/5 (0%), SVR24 13/14 (93%), EOT
6	1	Y	800	50 QOD	75	8	Enrolling (N=11)	9/10 (90%), SVR12*
7	1	Y	800	25 QD	75	8	Screening/Planned	N/A
8	1	Y	800	25 QD	75	8	Screening/Planned	N/A
9	1	Y	800	25 QD	75	12	Screening/Planned	N/A
10	1	Y	800	25 QD	75	12	Screening/Planned	N/A
11	2	Y	800	25 QD	75	12	Screening/Planned	N/A
12	2	Y	800	25 QD	75	8	Screening/Planned	N/A
12-15	TBD							

* Subject 11 has completed treatment. SVR visit results pending.

^ N=10-20 per cohort; In ongoing cohorts in which a dosing regimen is modified (e.g. treatment duration is extended) due to apparently insufficient efficacy/safety, the cohort size may be increased such that 20 subjects at the final dosing regimen are enrolled in that cohort.

This protocol permits enrollment of up to 16 cohorts. The maximum permissible enrollment in this study is up to 320 subjects.

Safety and tolerability will be evaluated on an ongoing basis through assessment of AEs, blood and urine sample analyses, collection of ECG, echocardiograms, vital signs and physical examinations. PK data will be routinely reviewed as it becomes available.

All enrolled subjects will be monitored from Day 1 through end of follow up for on treatment failure or relapse as defined by the criteria outlined in Sections 8.2.2–8.2.4. The Sponsor will provide the Investigator with the results of the resistance evaluation to enable them to evaluate the most appropriate therapeutic option for any subject that experiences relapse. Where necessary, the Sponsor will offer appropriate retreatment within a separate protocol or, if the subject is unable or unwilling to participate in that trial, the Sponsor will provide reimbursement for locally available HCV treatment for any subjects that experience on treatment failure or relapse, subject to local regulations. Alternatively, where possible, subjects will be allowed to enroll in a subsequent clinical trial subject to meeting the relevant entry criteria.

PK samples will be obtained at a single time point prior to dosing at all routine study visits while subjects are receiving study medication as well as at Weeks 3 and 6, 2-4 hours postdose, and at Weeks 4 and 8, 6-8 hours postdose. In addition, for a subgroup of up to 250 subjects, additional PK samples will be obtained at Week 2 for all treatment groups.

2.2 Study Schema

The study schema is presented in Figure 2-1. Study procedures are listed in Section 6.0 and depicted for the 8-week treatment group or 12-week treatment group in Table 6-1; the schedule of events for a 6-week treatment group can be found in Table 6-2 and for a 4-week treatment group in Table 6-3. A schedule for the post dosing follow-up period for all cohorts can be found in Table 6-4.

Figure 2-1 Study Schema

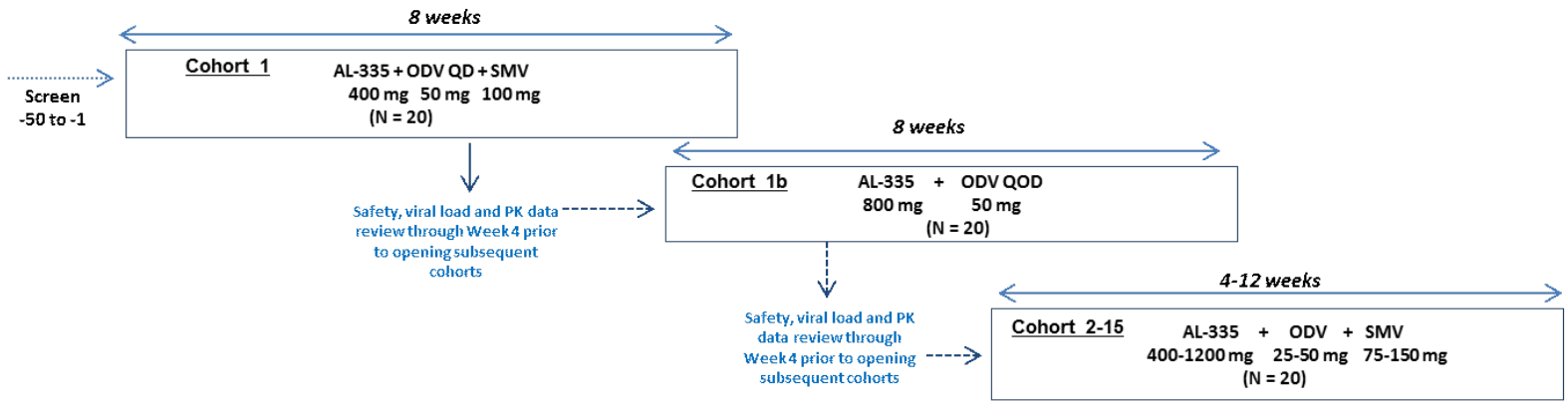

**Figure depicts range of permissible durations, total daily doses for each drug for cohorts 2-15. Based on emerging safety, pharmacokinetic, and efficacy data, the following study parameters may be changed for a given cohort after obtaining agreement from the Sponsor and the Investigator:

- Treatment duration: 4-12 weeks
- Doses
  - AL-335: 400-1200 mg
  - Odalasvir: 25-50mg (QD or QOD)
  - Simeprevir: 75-150 mg (if evaluated in a cohort)
- Genotype: Any combination of GT 1, 2 and 3
- Cohort size: 10-20 subjects. In ongoing cohorts in which a dosing regimen is modified (e.g. treatment duration is extended) due to apparently insufficient efficacy/safety, the cohort size may be increased such that 20 subjects at the final dosing regimen are enrolled in that cohort.
- Population: Treatment-naïve non-cirrhotic HCV-infected subjects and treatment naïve or treatment experienced HCV infected subjects with compensated cirrhosis (decompensated cirrhosis prohibited)
- Viral load: A viral load threshold may be included in determining eligibility for a cohort if higher viral loads are projected to have unacceptable efficacy. This threshold may be derived from emerging data (e.g. prior cohorts), medical literature, etc.

See Section 6.0 for details of Study Procedures.

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of AL-335 in combination with ODV with or without SMV in subjects with GT1 or GT2 or GT3 CHC infection

3.1.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To evaluate the efficacy of treatment with AL-335 in combination with ODV±SMV in subjects with GT1 or GT2 or GT3 CHC infection
- To evaluate the pharmacokinetics of AL-335 (and metabolites), ODV±SMV in plasma
- To evaluate the viral kinetics of HCV RNA in subjects with GT1 or GT2 or GT3 CHC infection treated with AL-335 in combination with ODV±SMV
- To evaluate the effect of baseline host and disease-related characteristics on treatment outcome
- To evaluate the impact of the presence of an (NS) 3 polymorphism (e.g., Q80K; SMV-containing arms only) and/or NS5A and NS5B polymorphisms at baseline on treatment outcome
- To evaluate the viral resistance profile after ≤12 weeks administration of AL-335 in combination with ODV±SMV

3.2 Study Endpoints

3.2.1 Primary Endpoint

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

3.2.2 Secondary Endpoints

- The proportion of subjects who have a sustained virologic response (SVR; i.e., HCV RNA concentration <LLOQ (<15 IU/mL) at 4, 8, 12, 18 and 24 weeks after the last actual dose of treatment
- PK parameters for AL-335 (and metabolites), ODV and SMV in plasma
- The proportion of subjects who experience virologic relapse during the follow-up period.
- The proportion of subjects who have on treatment failure while receiving study

medication

- Viral kinetics, as determined at different timepoints during treatment by the proportion of subjects who achieve
  - HCV RNA <LLOQ Undetectable
  - HCV RNA <LLOQ
- Time to achieve undetectable HCV RNA and <LLOQ HCV RNA
- The amino acid sequence of the NS5A, NS5B and NS3/4A proteins at baseline and post-baseline in subjects who fail treatment
- Effect of various baseline and host disease-related characteristics on treatment outcome

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Study Population

The target population will consist of treatment-naïve and treatment experienced male and female subjects (18-70 years of age, inclusive) with CHC infection. Up to 320 subjects will be enrolled into up to 16 treatment arms.

4.2 Inclusion Criteria

Main Inclusion Criteria for All Subjects:

1. Subject has provided written consent.
2. In the Investigator's opinion, the subject is able to understand and comply with protocol requirements, instructions, and protocol-stated restrictions and is likely to complete the study as planned.
3. Male or female, 18–70 years of age.
4. Body mass index (BMI) 18–35 kg/m^2, inclusive.
5. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin) pregnancy test at screening.
6. Female subjects must either:
   - not be of childbearing potential defined as:
     i. Postmenopausal for at least 12 months (i.e., 2 years of amenorrhea without an alternative medical cause) and a serum follicle stimulating hormone (FSH) level in the postmenopausal range (per reference laboratory), OR
     ii. Surgically sterile (e.g., underwent total hysterectomy, bilateral oophorectomy, or bilateral tubal ligation/bilateral tubal clips without reversal operation), or otherwise incapable of becoming pregnant,
   - OR

i. be of childbearing potential AND

ii. not heterosexually active (e.g., abstinent or homosexual) from screening until 6 months after study drug administration (or longer, if dictated by local regulations), OR

iii. if heterosexually active

- have a vasectomized partner (confirmed sterile per verbal account of the subject), OR
- using an acceptable method of birth control from screening and agree to continue to use the same method of contraception throughout the study and for 6 months after study drug administration (or longer, if dictated by local regulations). Acceptable methods of birth control include: oral hormone-based contraceptives, an IUD, being either hormonal (i.e., IUS) or non-hormonal, other non-oral hormone-based contraception methods (e.g., injectable, implants, transdermal system, vaginal ring), or a double-barrier method (eg, male condom + either a diaphragm or cervical cap with or without spermicide). Condom use by male partners with reproductive potential is required in all circumstances except when female subjects are using acceptable birth control methods which are long term in nature and do not require high degrees of compliance (e.g. IUDs, depot-form injectables, implants).
- See also the NOTES regarding contraception considerations that apply to men and women at the bottom of Inclusion #7

7. Male subjects must either:

- be surgically sterile (had a vasectomy), or otherwise incapable of fathering a child, OR
- not be heterosexually active (e.g., abstinent or homosexual) from enrollment (Day 1) in the study until at least 6 months after study drug administration, OR
- if heterosexually active:
  - have a partner who is postmenopausal (2 years amenorrhea), surgically sterile (e.g., has had a total hysterectomy, bilateral oophorectomy, or bilateral tubal ligation/bilateral tubal clips without reversal operation), or otherwise incapable of becoming pregnant OR
  - be practicing an acceptable method of birth control from enrollment in the study (Day 1) and agree to continue to use the same method of contraception throughout the study and for at least 6 months after study drug administration (or longer, if dictated by local regulations). An acceptable method of birth

control for male subjects is a double-barrier method (e.g., male condom+either diaphragm or cervical cap with or without spermicide).

NOTE 1: Male subjects with a female partner who uses hormonal contraceptives (oral, injectable, implants) or a hormonal (IUS) or non-hormonal IUD and male subjects who are vasectomized or otherwise incapable of fathering a child are not required to use additional contraceptive methods.

NOTE 2: 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 3: A male and female condom should not be used together due to risk of breakage or damage caused by latex friction.

NOTE 4: Contraceptive use by men and 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.

8. Subjects must agree to refrain from sperm/egg donation from start of dosing through 6 months after the completion of study drug administration.
9. GT1a or 1b or GT2 or 3 CHC, depending on cohort, with positive HCV antibody and a positive HCV RNA at screening including documentation of CHC infection for at least 6 months. Genotype testing must occur at a screening visit. NOTE: GT1 patients are eligible for inclusion even if they cannot be successfully subtyped unless a specific subtype is required for a cohort.
10. Screening HCV RNA viral load ≥50,000 IU/mL, except for subjects with compensated cirrhosis (Child-Pugh Class A) who may have HCV RNA viral load $\geq 10^4$ IU/mL.
11. Treatment naïve (i.e., no prior exposure to any approved or investigational drug(s) including direct-acting antivirals, and interferon-based treatment regimens) or, in subjects with cirrhosis, treatment experienced (defined as subjects who experienced virologic relapse after receiving a full course of pegylated interferon+ribavirin (peg/riba) treatment). Prior use of any direct acting antiviral in combination with peg/riba is not permitted.
12. Fibroscan, collected within 6 months of baseline visit, with liver stiffness score ≤12.5 kPa to be eligible (except for subjects with cirrhosis, see below).
    - Subjects with compensated cirrhosis must meet the Child-Pugh Class A definition (see Appendix G) and at least one of the following criteria:

iii. Liver biopsy result indicating the presence of cirrhosis (e.g., Metavir F4; Ishak >5) or
iv. Fibroscan evaluation with a liver stiffness score >12.5 kPa

13. Subject is otherwise in good health as deemed by the investigator, based on the findings of a medical evaluation including medical history, physical examination, laboratory tests and ECG.
14. Willing to avoid prolonged sun exposure and use of tanning devices while taking SMV and through 4 weeks of follow up. Subjects should also be advised to use a broad-spectrum sunscreen and lip balm of at least sun protection factor >30 to help protect against potential sunburn.

4.3 Exclusion Criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Pregnant, planning on becoming pregnant (during treatment and up to 6 months after the EOT), or breast-feeding female subject, or male subject whose female partner is pregnant or planning on becoming pregnant (during treatment and up to 6 months after the EOT)
2. Other than CHC with or without compensated cirrhosis, clinically significant cardiovascular, respiratory, renal, gastrointestinal, hematologic, neurologic, thyroid or any other medical illness or psychiatric disorder, as determined by the Investigator and/or Sponsor's Medical Monitor.
3. History or other clinical evidence of significant or unstable cardiac disease (e.g., angina, congestive heart failure, myocardial infarction, diastolic dysfunction, significant arrhythmia, coronary heart disease, and/or clinically significant ECG abnormalities), moderate to severe valvular disease or uncontrolled hypertension at screening.
4. Screening echocardiogram ejection fraction <55% or any other echocardiographic finding suggestive of clinically relevant cardiomyopathy.
5. Creatinine clearance of <60 mL/min (Cockcroft-Gault).
6. Positive test for HAV IgM, HBsAg, or HIV Ab.
7. Abnormal screening laboratory results that are considered clinically significant by the investigator.
8. History of clinical hepatic decompensation, e.g., variceal bleeding, spontaneous bacterial peritonitis, ascites, hepatic encephalopathy or active jaundice within the last year.
9. Any condition that, in the opinion of the investigator, would compromise the study's objectives or the well-being of the subject or prevent the subject from meeting the study requirements.

10. Participation in an investigational drug trial or having received an investigational vaccine within 30 days or 5 half-lives (whichever is longer) prior to study medication.
11. Clinically significant abnormal screening ECG findings (e.g., PR >200 msec, QRS interval >120 msec or corrected QT interval (QTc) >450 msec for male subjects and >470 msec for female subjects), based on an average of triplicate ECGs. Any evidence of heart block or bundle branch block is also exclusionary.
12. History or family history of abnormal ECG intervals, for example prolonged QT syndrome (*torsade de pointes*) or sudden cardiac death.
13. The subject has a positive prestudy drug screen, including methadone unless the drug is prescribed by the subject's physician. The list of drugs that should be screened for includes amphetamines, barbiturates, cocaine, opiates, phencyclidine (PCP), and benzodiazepines. Drug use without a physician prescription may be permitted on a case by case basis after review by the Sponsor in consultation with the investigator.
14. Laboratory abnormalities including:
    - Hematocrit <0.34
    - White blood cell counts <3,500/mm^3 (<1,000/mm^3 for subjects with compensated cirrhosis)
    - Absolute neutrophil count <1,000/mm^3 (<750/mm^3 for subjects with compensated cirrhosis)
    - Platelets ≤120,000/mm^3 (platelets <70,000/mm^3 for subjects with compensated cirrhosis)
    - Glycosylated hemoglobin (HbA1C) >55 mmol/mol or 7.2%
    - Prothrombin time ≥1.5 × ULN
    - Albumin ≤32 g/L, bilirubin ≥1.5 mg/dL at screening (subjects with documented Gilbert's disease allowed)
    - Serum ALT concentration ≥5× ULN
    - CK >1.5× ULN

    A single repeat laboratory evaluation under appropriate conditions (e.g., fasted, no antecedent exercise) is allowed for eligibility determination.
15. Any condition possibly affecting drug absorption (e.g., gastrectomy or other significant gastrointestinal tract surgery, such as gastroenterostomy, small bowel resection, or active enterostomy).
16. Clinically significant blood loss or elective blood donation of significant volume (i.e., >500 mL) within 60 days of first dose of study drug; >1 unit of plasma within 7 days of first dose of study drug.

17. Evidence of clinically relevant active infection that would interfere with study conduct or its interpretation.
18. History of regular alcohol intake >10 standard drinks per week of alcohol for females and >15 standard drinks per week for males (one unit is defined as 10 g alcohol) within 3 months of the screening visit.
19. The use of prohibited medications, including prescription, over-the-counter (OTC) medications, herbal medications, inducers or inhibitors of CYP450 enzymes or drug transporters (including P-gp) within 14 days prior to the first dose of study medication is excluded, unless previously approved by the Sponsor's Medical Monitor. NOTE: Chronic medication use is permitted so long as they are medically necessary, deemed acceptable by the Principal Investigator and Medical Monitor, and not Prohibited Medications (see Section 5.12).
20. Hypersensitivity to the active substances (including sulfa allergy) or to any of the excipients of AL-335, ODV or SMV.
21. Evidence on recent (within 6 months) liver ultrasound of hepatic mass or lesion concerning for malignancy (subjects with cirrhosis only).

4.4 Subject Screening and Enrollment

Screening procedures will occur when a subject signs and dates an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Ethics Committee (EC) approved informed consent form (ICF) and provides authorization to use protected health information. The ICF will be completed prior to any study-specific procedures. The use of a site-specific generic consent form, approved by the local EC, may be used prior to approval of the study specific consent form at the Sponsor's discretion.

To enroll, the investigator will verify eligibility according to all inclusion and exclusion criteria (Sections 4.2 and 4.3). Any questions regarding eligibility should be addressed to the Sponsor's Medical Monitor prior to enrollment.

4.4.1 Screening Examination

A screening examination should be performed between -50 and -1 days before the start of the study. Subjects must fulfill all entry criteria to be accepted into the study.

A screen failure log must be maintained by the investigator.

At the screening examination, the procedures outlined in Table 6-1 through Table 6-3 will be performed to establish each candidate's general health and qualifications for enrollment into the study.

For re-screened subjects who were previously screened in the study and found to be eligible but were not enrolled due to limited cohort slot enrollment availability or other nonmedical reasons or were ineligible under a prior protocol version but became eligible under an approved later

version of the protocol, the screening procedures outlined in Table 6-1 through Table 6-3 should be repeated with the exclusion of the following:

- Echocardiogram (as long as the most recent study echocardiogram was obtained within the past 4 months)
- HCV genotype
- Hepatitis and HIV screen
- IL28B genotype

4.5 Subject Completion

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

4.6 Subject Discontinuation

The primary consideration in any determination to discontinue a subject's participation must be the health and welfare of the subject. Reasons for discontinuation may include, but are not limited, to the following:

- An AE or SAE, drug reaction, or complication, whether related or not to study drug, which precludes continuation of treatment with study drug. This includes the development of allergic reactions or other potentially serious drug reactions to the study medication.
- Noncompliance with study drug dosing.
- Noncompliance with study procedures.
- Lost to follow up.
- Subject's right to withdraw consent at any time during the study, with or without a stated reason.
- The principal investigator's opinion that it is not in the subject's best interest to continue study participation.
- Sponsor's decision to terminate the study (e.g., see section 4.7).

Subjects are free to discontinue their participation at any time during this clinical trial. The investigator has the right to remove any subject from treatment with study drug or participation in the study. However, Alios requests that the investigator consult with the Sponsor's Medical Monitor before prematurely removing a subject. For subjects that discontinue study drug prematurely, sites are strongly encouraged to follow these subjects as prescribed in this protocol as much as possible as this is the primary mechanism to ensure subject safety.

Any subject who decides to discontinue participation in the study, or meets the discontinuation criteria specified below, should undergo early discontinuation procedures (Section 4.6.2).

4.6.1 Subject Treatment Discontinuation Criteria

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

A subject's study drug treatment (AL-335, SMV and ODV) must be permanently discontinued if:

- The investigator believes that for safety reasons (e.g., AE), it is in the best interest of the subject to discontinue study drug treatment.
- The subject becomes pregnant.
- The subject has evidence of muscle injury (Section 7.5.1) or cardiac toxicity (Section 7.5.2 and 7.5.3).
- The subject has a Grade 4 rash; see Section 7.6.
- The subject has a Grade 3 or 4 allergic reaction; see Section 7.7.
- The subject has a confirmed Grade 4 ALT and/or AST value that is >2× the baseline value; see Section 7.9.
- The subject has a confirmed Grade 4 bilirubin value which is considered a sign of worsening liver disease, or for which there is no identifiable explanation; see Sections 7.8 and 7.9.
- The subject has severe worsening of hepatic disease.
- The subject has a confirmed diagnosis of pancreatitis.
- The subject has a Grade 4 AE or laboratory abnormality at least possibly related to 1 of the study drugs and which is considered clinically significant (laboratory abnormalities only).
- The subject requires treatment with any of the medications reported on the list of disallowed medications; see Section 5.12.
- The subject experiences inadequate virologic response or viral breakthrough (refer to Definitions)
- An event occurs which triggers the study treatment stopping criteria (Section 4.7.1)

4.6.2 Procedures for Subjects Who Discontinue Treatment

Subjects who discontinue from treatment should undergo the Study Completion procedures tabulated in Section 6.1 for the purpose of safety monitoring within 7 days after their last dose of study medication. Any subject that discontinues with ongoing AEs should be followed until resolution of their AE(s) or until the investigator has determined that the AE(s) has stabilized. In addition subjects should be followed up per Table 6-4 off treatment for up to 24 weeks, or when commencing therapy if earlier.

4.6.3 Withdrawal from the Study

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

- Lost to follow up
- Withdrawal of consent
- Death

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. Subjects who withdraw consent during the treatment or follow-up phase will be offered an optional safety follow-up visit, at which the assessments from the Week 4 follow-up visit need to be performed.

Subjects who withdraw consent from the PK substudy (see Section 6.2.1) can still continue to participate in the main study. If the subject enrolls in a clinical study with an investigational drug (including investigational vaccines), the subject will have to withdraw from the current study first.

Subjects who discontinue may withdraw consent for use of their samples for future research (refer to Section 11.7). 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.

4.6.4 Documentation of Discontinuation of Subjects

Document the reasons for early discontinuation of any subject from the study on the appropriate case report form (CRF). If the reason for early discontinuation is an AE or an abnormal laboratory value, record the specific event or test result on the AE CRF, and monitor the subject until the event is resolved or deemed stable by the investigator.

4.7 Study Discontinuation

The Sponsor has the right to terminate this study or remove a participating site at any time. Reasons for terminating the study or site may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects as described in section 4.7.1 Study Treatment Stopping Criteria.
- Subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.
- A decision from the IRB/IEC, or regulatory authority to terminate the study.
- The Sponsor may also opt to not conduct any of Cohorts7–15 if they are considered redundant or to otherwise not contribute to the achievement of the study's objectives.

4.7.1 Study Treatment Stopping Criteria

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 current study if adjudicated by the Sponsor, in consultation with the Investigator, 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 Sponsor in consultation with the Investigator will take place within 72 hrs 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.

4.8 Futility Criteria

4.8.1 Predefined Criteria to Determine the Futility of an Individual Treatment Regimen

The futility of any of the regimens evaluated in the study will be assessed by the Sponsor based on predefined criteria, as detailed below. Once a predefined futility criterion is met, appropriate action will be taken by the Sponsor, which may include halting the enrollment of individual treatment arms and/or extending treatment duration of subjects who have not yet reached end of treatment at that time. Futility criteria will be in place during the entire conduct of the study. The Sponsor will evaluate the futility criteria and notify the Principal Investigator if a futility criterion is met.

The objective of the futility criteria is to detect futile regimens as early as possible and ideally within a timeframe that would allow the Sponsor to take action (i.e., while recruitment or treatment phase is ongoing). The futility criteria will take into account post-treatment failure for virologic reasons (viral relapse; see Definitions of Terms). For confirmation of viral relapse, an HCV RNA retest should be scheduled (see Sections 6.2.3 and 6.2.4). However, the Sponsor may evaluate futility criteria based on the original test results without waiting for the retest results.

The futility criteria will have been met:

- If >2 subjects in any 1 cohort experience viral breakthrough or inadequate virologic responsewhile recruitment is ongoing. Further recruitment in the cohort will then be discontinued
- If ~15% of subjects in a cohort experience relapse at any available timepoint during the follow-up phase (at 24 weeks after actual end of study drug treatment or earlier for subjects who have not yet reached the 24 weeks after actual end of study drug treatment visit).

If the futility criterion is met for a regimen evaluated in a historically easier to treat population (e.g., subjects with GT1 infection without cirrhosis), then that regimen will not be evaluated in historically more difficult to treat populations (e.g., subjects with GT1 infection and with cirrhosis).

If a drug regimen evaluating a particular treatment duration is found to be futile in a population, a shorter duration of that drug regimen will not be assessed in that population. Also, shorter duration cohorts (e.g., 6 weeks) will only be initiated if supported by viral kinetic data from longer duration cohorts in the same patient population. Supportive data are defined as viral load below the limit of quantification for ≥80% of subjects at Week 6 in an 8-week cohort. A similar paradigm will be applied for cohorts of 4 weeks' duration based on 4-week data from cohorts of 6 weeks' duration.

5.0 DOSING REGIMEN

5.1 Rationale for Dosage Selection

5.1.1 AL-335

A dose of 400 to 1,200 mg qd for AL-335 has been selected for this study. These doses are based on safety and PK data from Study AL-335-601 (Section 1.2.1.1), Study AL-335-602 (Section 1.2.1.2), and preliminary data from Cohorts 1-3 in Study AL-335-604 (Section 1.2.1.2). In these studies, single and multiple doses up to 1,200 mg have been well tolerated and preliminary information on the impact of ODV and SMV dosing on the pharmacokinetics of AL-335 and its metabolites is known.

Evaluation of higher doses of AL-335 up to 1,200 mg qd is considered justified because:

- AL-335 and its metabolite exposures appear to increase less than dose proportionally for AL-335 doses >800 mg
- Higher doses of AL-335 may be needed to increase antiviral activity
- It is anticipated that the 1,200 mg qd dose of AL-335, even in the setting of a drug–drug interaction with SMV and/or ODV, will deliver mean projected exposure of ALS-022227 that will not exceed the NOAEL established in nonclinical studies.
- The safety and pharmacokinetics of a dose that will deliver exposures ≤2-fold those already evaluated in this and earlier studies can be safely evaluated in this study given the intensive nature of the safety/PK assessments defined in the Schedule of Events (Section 6.0).

5.1.2 Simeprevir

A dose of 75 to 150 mg for SMV has been selected for this study. In a drug-drug interaction study in healthy volunteers (AL-335-602), PK results suggest ODV increases SMV exposure (AUC) 1.8-fold. It is anticipated that the 100 mg dose of SMV, along with the interaction of ODV, will result in exposures of SMV approximately similar to 150 mg (the approved dose) without interaction; a dose that has demonstrated to be efficacious and well tolerated in patients with CHC. Similarly, it is anticipated that the 75 mg dose of SMV, along with the interaction of ODV, will result in exposures of SMV approximately similar to 100 mg (the approved dose in Japan) without interaction; this dose has also been demonstrated to be efficacious and well tolerated in patients with CHC. For a 150 mg dose of SMV, even in the setting of a drug-drug interaction with ODV, the projected SMV exposures are expected to be within the range of

exposures seen in patients with mild (Child Pugh A) cirrhosis, a population in which the 150 mg SMV dose is approved without dose adjustment.

5.1.3 Odalasvir

A daily dose of 12.5 to 50 mg for ODV has been selected for this study. In prior studies, a 50 mg daily dose of ODV given as a liquid filled capsule has been shown to be well tolerated and have clinical efficacy in combination with another nucleotide (sofosbuvir) in patients infected with HCV. Also, when a liquid filled capsule of ODV was given as monotherapy in a prior study, a single dose of 25 to 300 mg demonstrated similar antiviral effects. Taken into account these data and emerging efficacy data from Study AL-335-604, it is possible total daily doses <25 mg of ODV administered as a tablet may also be efficacious. Because only 25-mg and 50-mg ODV tablets are available for this study, dosing with 25 mg ODV qod may be administered if a decision is made to evaluate the efficacy of ODV using the equivalent of a 12.5 mg daily dose.

5.1.4 Dosing Regimens for Patients With Mild (Child Pugh A) Cirrhosis

AL-335 and its metabolites appear to have similar steady state exposures in cirrhotic vs, non-cirrhotic patients (Study AL-335-601). Furthermore the 800 mg dose of AL-335 has been well tolerated and may deliver more antiviral activity than a 400 mg dose (see Section 1.2.1.1). As a result, the AL-335 dose for the first cohort of subjects with cirrhosis will be 800 mg qd.

ODV has not been studied in CHC subjects with compensated cirrhosis; however, other drugs in the same drug class are known to have lower exposures in patients with cirrhosis compared to patients without cirrhosis. As a result, it is not expected that a 50 mg dose of ODV will deliver higher exposures in patients with vs. those without cirrhosis. Nevertheless, as a precaution, the ODV dose for the first cohort of subjects with cirrhosis will be 25 mg qd or 50 mg qod.

Because SMV is primarily cleared by the liver, the SMV dose for the first cohort of subjects with cirrhosis will be the lowest possible qd dose (75 mg).

After the safety and PK data of all 3 drugs has been evaluated in the first cohort of subjects with compensated cirrhosis, the dose limits defined in Sections 5.1.1 through 5.1.3 may then be explored if supported by emerging data.

5.2 Description of Study Drug and Background Therapy

5.2.1 AL-335

AL-335 will be supplied as tablets containing 400 mg of AL-335 and microcrystalline cellulose (filler), croscarmellose sodium (disintegrant), and magnesium stearate (lubricant). A second formulation of AL-335 may be supplied as well and these tablets contain 100 mg of AL-335 and microcrystalline cellulose (filler), croscarmellose sodium (disintegrant), and magnesium stearate (lubricant). AL-335 will be supplied to the site in open-label containers and stored at controlled room temperature.

5.2.2 Simeprevir

SMV 75 mg capsules will be supplied as red hard gelatin capsules. SMV 100 mg capsules will be supplied as hard gelatin, white capsules with black "TMC435" print. SMV 150 mg capsules

will be supplied as hard gelatin, white capsules with black "TMC435 150" print. Each capsule contains 75, 100, or 150 mg of SMV along with sodium lauryl sulphate, magnesium stearate, anhydrous colloidal silica, croscarmellose sodium, and lactose monohydrate. SMV capsules will be supplied to the site in open-label containers and stored at controlled room temperature.

5.2.3 Odalasvir

ODV will be supplied as film-coated tablets containing 25 or 50 mg of ODV active drug substance, poloxamer 407, copovidone, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate and white film coating (polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, and talc).

5.3 Dose Preparation and Administration

Study medication will be dispensed by the licensed investigational pharmacist or other authorized personnel with appropriate training.

Subjects will be told to take each dose of AL-335, SMV, or ODV with food (or up to 15 minutes after completion of a meal) once a day at approximately the same time each day. On Day 1, study medication should be administered after all baseline assessments have been completed. On subsequent study visits where biochemistry assessments are scheduled, subjects will be required to fast for at least 8 hours overnight. Subjects will receive study medications at the clinical trial site after receiving a meal following the biochemistry blood draw.

5.4 Treatment Delay or Interruption

No treatment delay or interruptions are allowed without consultation of the Sponsor's Medical Monitor.

5.5 Missed Doses

In the event of a missed dose, after discussion with the Sponsor Medical Monitor, a subject's study drug regimen may be resumed if the proposed time of administration of study drug is ≤12 hours since the planned time of the missed dose for AL-335, SMV, or ODV. If more than 12 hours (AL-335, SMV, ODV) have passed since the missed dose, the subject should skip the missed dose and resume dosing at the next planned time.

5.6 Overdoses

In the event that a subject takes an accidental overdose of ≤200% of the planned dose and the subject is asymptomatic and deemed clinically stable, continued dosing is permissible after a discussion with the Sponsor Medical Monitor.

5.7 Dose Modifications

The dose of AL-335, SMV or ODV may be modified in subsequent cohorts based on safety, efficacy and PK data from prior cohorts. Cohorts 1b, 2 to 15 may or may not include SMV. Mean projected plasma exposures of ALS-022399, ALS-022227, and ODV at the doses selected in study cohorts will not exceed NOAEL exposures obtained from nonclinical toxicology studies. SMV doses will not exceed the approved dose.

If any of the individual study drugs is discontinued, unless specific requirements are already defined in this protocol, the investigator must contact the Medical Monitor to assess the need to stop all study drugs.

5.8 Ordering Study Drug

To order study drug, refer to the Pharmacy Manual.

5.9 Drug Accountability

Study site personnel will maintain adequate records of the receipt and disposition of all study medication shipped to the site. Records must include dates, lot numbers, quantities received, quantities dispensed and the identification number of each subject who has received each lot of study drug.

The investigator will not supply study drug to any person not authorized to receive it.

5.10 Disposition of Used, Partially Used, and Unused Study Medication Containers

All used and unused study drug supplied by Alios BioPharma must be retained by the pharmacist. Periodically throughout and at the conclusion (or suspension, termination, or discontinuation) of the study, a representative of Alios BioPharma or its designated agent will conduct inventories and accountability of study materials. Once accountability is completed, an Alios BioPharma representative or designee will authorize the return of all used and unused study medication containers to a designated facility. For study medication containers returned to Alios BioPharma or its designated agent, records will include dates, lot numbers, and quantities of study drug returned. Local destruction of study drug is permitted where appropriate methods of destruction are available.

5.11 Concomitant Medications

Medications not explicitly prohibited (see Section 5.12) may be used as concomitant medications, where the investigator feels it appropriate to do so. For analgesia and anti-pyretic therapy, investigators are encouraged to use low doses of ibuprofen (or equivalent) on an as needed basis. Questions related to medications to treat AEs should be discussed with the medical monitor, whenever feasible, to minimize the risk of unintended drug–drug interactions. All medications, prescription and OTC, including vitamins and herbal products taken within 30 days of study screening and during the study, will be recorded in the CRF with indication, dose information and dates of administration.

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

ODV has demonstrated a low inhibition potential for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A. ODV is primarily cleared by biliary secretion, is not significantly metabolized, and is not expected to be involved with clinically significant

drug-drug interaction associated with the CYP enzyme system. ODV is neither a substrate nor an inhibitor of transporters such as OATP1B1/3, BCRP, MRP2, MRP3, and BSEP. ODV is a low-affinity substrate of OATP1B1. ODV is not a substrate but is an inhibitor of P-gp. Co-administration of ODV with drugs that are substrates for P-gp transport may result in increased plasma concentrations of such drugs.

SMV is a mild inhibitor of intestinal CYP3A. Co-administration of SMV with drugs that are primarily metabolized by CYP3A may result in mild increases in plasma concentrations of such drugs, which could increase or prolong therapeutic effect and adverse reactions of CYP3A substrates with narrow therapeutic index. Drugs that induce CYP3A may decrease SMV plasma concentrations and reduce the therapeutic effect of SMV. Co-administration of SMV with inhibitors of CYP3A may increase SMV plasma concentrations. Clinically, SMV inhibits uptake transporters OATP1B1/3 and the efflux transporters P-gp/MDR1 and MRP2. Co-administration of SMV with drugs that are substrates for OATP1B1/3, and P-gp transport may result in increased plasma concentrations of such drugs.

The concomitant medications in Table 5-1 are allowed, but should be used with caution and be administered at the lowest possible dose, with monitoring of AEs and desired efficacy.

Table 5-1. Concomitant Medication to be Administered With Caution

- P-gp substrates with a narrow therapeutic index
- Acid-reducing agents - antacids (e.g., aluminum and magnesium hydroxide) should be administered 4 hours apart; H_2-receptor antagonists (e.g., cimetidine, famotidine, nizatidine, ranitidine) may be administered simultaneously with or 12 hours apart from study drugs at a dose that does not exceed doses comparable to famotidine 40 mg twice daily)
- Analgesics: ergaloid mesylates, ergotamine tartrate, dihydroergotamine, and methylergonovine
- Lipid-lowering drugs - atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin
- Phosphodiesterase type 5 inhibitors - sildenafil, tadalafil, vardenafil
- Sedatives/anxiolytics - lorazepam, midazolam, oxazepam, triazolam
- Warfarin

Note: This list of permitted (with caution) medications is subject to change based on emerging information related to the study drugs (e.g., transporter study results) or other medications (e.g., new information from the medical literature). The most up-to-date list of permitted (with caution) medications can be found in the study manual or a note to file.

5.12 Prohibited Medications

An overview of prohibited medications is presented in Table 5-2.

Table 5-2. Prohibited Medications

Prohibited Medications include potent and moderate CYP3A4 inducers/inhibitors, P-gp inhibitors, CYP3A substrates with a narrow therapeutic index, and drugs known to prolong the QT interval. Drugs in these categories and which are prohibited include (by class)
• Anti-arrhythmics – amiodarone (prohibited from 3 months prior to first dose), digoxin, disopyramide, dronedarone, flecainide, mexilitine, systemic lidocaine, propafenone, quinidine
• Anti-epileptics - carbamazepine, oxcarbazapine, (fos)phenytoin, phenobarbital
• Anti-infectives - clarithromycin, erythromycin, fluconazole, itraconazole, posaconazole, telithromycin, troleandomycin, voriconazole
• Antiretrovirals - atazanavir, cobicistat, delavirdine, darunavir, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, tipranavir
• Anti-tuberculosis drugs - rifabutin, rifampin, rifapentine
• Beta-blockers
• Calcium-channel blockers - amlodipine, bepridil, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil
• Immunomodulators - cyclosporine, interleukins, or systemic corticosteroids at an immunosuppressive dose
• Dexamethasone (if administered systemically and more than one dose)
• Antihistamines - astemizole, terfenadine
• Cisapride
• Proton pump inhibitors -(dex)lansoprazole, (es)-omeprazole, pantoprazole, rabeprazole
• Herbal or nutritional products intended for liver disease including HCV (e.g., silibinin, silybin, silymarin (milk thistle))
• Miscellaneous - products containing *Hypericum perforatum* (St. John's Wort)

Note: The list of prohibited 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.

These medications are prohibited from 14 days prior to initiation of treatment through the last study visit with the exception of amiodarone (prohibited from 3 months prior to first dose). Subjects that receive a prohibited medication should be discussed as soon as practical with the Medical Monitor. Study treatment may be discontinued if a subject receives a prohibited medication. Subjects that discontinue study drug due to use of a prohibited medication will be followed up as outlined in Section 4.6.1.

In addition to the medications outlined in Table 5-2, drugs which are known to prolong the QTc interval (see https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf) may not be initiated once a subject has begun study drug treatment unless the medication is necessary to protect subject safety and it has been discussed with the Sponsor. An ECG should be performed prior to initiating any drugs which may prolong the QTc interval. Drugs which prolong the QTc (e.g., methadone, citalopram) are permitted as prior/concomitant medications if they have been administered chronically (at least 2 months prior to enrollment), the dose is stable (for at least 4 weeks prior to enrolling), and the subject's QTc interval is normal (see Inclusion/Exclusion criteria).

Note: The list of prohibited medications in Table 5-2 is subject to change based on emerging information related to the study drugs (e.g., transporter study results) or other medications (e.g., new information from the medical literature). The most up to date list of prohibited/concomitant medications can be found in the study manual or a note to file.

5.13 Special precautions

SMV is known to be associated with rashes including photosensitivity reactions. Investigators must advise study participants taking SMV of the need to avoid prolonged sun exposure or tanning devices. When these subjects are exposed to sunlight they should take appropriate precautions (examples include long sleeve shirts, long pants, hats, sunscreen with sun protection factor >30).

5.14 Special Dietary Requirements

During the study, subjects will be advised to adhere to the following dietary requirements:

- Subjects should be requested to refrain from significant alcohol consumption from screening up to and including the Week 12 follow-up visit.
- Grapefruit, grapefruit juice, and seville orange will not be permitted within 14 days prior to administration of study drug(s) (Day 1) and throughout the study until follow-up Week 4.
- Subjects should be requested to refrain from any strenuous activities through study follow-up Week 4. Light ambulatory activities will be permitted.

6.0 STUDY PROCEDURES

6.1 Schedule of Events

Table 6-1. Schedule of Events for 8 or 12*-Week Treatment Groups

Interval / Assessments	Day				Week**							
	Screen -50 to -1	1	2	3	1	2	3	4	5	6	7	8
AL-335+ODV±SMV [1]		< ----------										---------->
Obtain informed consent before study procedures	X											
Demographics	X											
Height, Weight, BMI[2]	X											X [2]
Drug Screen	X											
Medical History	X											
Echocardiogram	X							X (±3 days)				X (±3 days)
Triplicate 12-Lead electrocardiogram	X	X			X	X	X	X	X	X	X	X
Physical Exam and vital signs [3]	X	X			X	X	X	X	X	X	X	X
Hepatitis and HIV screen (HBsAg, HBsAB, HBcAb, HCVAb, HIVAb)	X											
Alpha-fetoprotein, glycosylated HbA1C	X											
Liver Ultrasound (subjects with cirrhosis)	X											
HCV genotype	X											
IL28B genotype		X										
Enrollment [4]		**X**										
AE & Conmed Evaluation	X	X	X	X	X	X	X	X	X	X	X	X

[1] Cohorts 1b, 2 to 16 may or may not include SMV. Dosing frequency will be qd except possibly for ODV which may also be dosed qod.
[2] Weight only collected at last treatment visit.
[3] Complete Physical Exams, including vital signs (BP, HR, RR, body temperature), are to be done at screening, predose on Day 1, early termination, safety follow-up visits. Symptom directed physical exams and vitals are to be collected as necessary at all other visits.
[4] Enrollment may take place up to 4 days before first dose.

Table 6-1. Schedule of Events for 8 or 12*-Week Treatment Groups

Interval / Assessments	Day				Week**							
	Screen -50 to -1	1	2	3	1	2	3	4	5	6	7	8
PK Samples [5]		X				X	X	X		X		X
Hematology [6]	X	X			X	X		X		X		X
Serum Chemistries [6]	X	X			X	X		X		X		X
Urinalysis	X	X			X	X		X		X		X
ALT/AST [6]	X	X			X	X	X	X	X	X	X	X
HCV RNA concentrations [7]	X	X	X	X	X	X	X	X	X	X	X	X
Plasma for drug resistance monitoring [8]		X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test [9]	X							X				X
Optional stored serum sample [10]	X	X			X	X	X	X	X	X	X	X

[5] A single predose PK sample will be collected at each indicated visit for AL-335 (and metabolites), ODV and SMV concentrations for all subjects. In addition, PK samples will be collected at Weeks 3 and 6, 2-4 hours postdose, and at Weeks 4 and 8, 6-8 hours postdose. Subjects in the intensive PK subset will have the following samples collected at the Week 2 visit Predose (within 0.5 hour) and 0.5, 1, 2, 3, 4, 6, 9, and 24 hours postdose.

[6] Blood for routine safety evaluations should be collected in a fasted state.

[7] Plasma for HCV RNA analysis to be collected predose at Day 1.

[8] Plasma collected for HCV RNA resistance monitoring will be collected at the same time as HCV RNA quantification. The Day 1 samples must be collected predose.

[9] Heterosexually active women of childbearing potential. A highly sensitive pregnancy test (e.g., urine or plasma) must be conducted immediately (within 4 days) prior to initiating treatment on Day 1 (local results may be used for this eligibility determination)

[10] For additional safety investigations as needed.

* If a 12-week regimen is evaluated, the Week 5, 6, 7, and 8 visits will be repeated at Weeks 9, 10, 11, and 12, respectively.

** Weekly visit may occur ±1 day from the expected visit date.

Table 6-2. Schedule of Events for a 6-Week Treatment Group

Interval / Assessments	Day				Week*					
	Screen -50 to -1	1	2	3	1	2	3	4	5	6
AL-335+ODV±SMV [1]		< ----------								---------->
Obtain informed consent before study procedures	X									
Demographics	X									
Height, Weight, BMI [2]	X									X [2]
Drug Screen	X									
Medical History	X									
Echocardiogram	X (±3 days)							X (±3 days)		X (±3 days)
Triplicate 12-Lead electrocardiogram	X	X			X	X	X	X	X	X
Physical Exam and vital signs [3]	X	X			X	X	X	X	X	X
Hepatitis and HIV screen (HBsAg, HBsAB, HBcAb, HCVAb, HIVAb)	X									
Alpha-fetoprotein, glycosylated HbA1C	X									
HCV genotype	X									
IL28B genotype		X								
Enrollment [4]		**X**								
AE & Conmed Evaluation	X	X	X	X	X	X	X	X	X	X

[1] Cohorts 1b, 2 to 16 may or may not include SMV. Dosing frequency will be qd except possibly for ODV which may also be dosed qod.

[2] Weight only collected at Week 6.

[3] Complete Physical Exams, including vital signs (BP, HR, RR, body temperature), are to be done at screening, predose on Day 1, early termination, safety follow-up visits. Symptom directed physical exams and vitals are to be collected as necessary at all other visits.

[4] Enrollment may take place up to 4 days before first dose.

Table 6-2. Schedule of Events for a 6-Week Treatment Group

Interval / Assessments	Day				Week*					
	Screen -50 to -1	1	2	3	1	2	3	4	5	6
PK Samples [5]		X				X	X	X		X
Hematology [6]	X	X			X	X		X		X
Serum Chemistries [6]	X	X			X	X		X		X
Urinalysis	X	X			X	X		X		X
ALT/AST [6]	X	X			X	X	X	X	X	X
HCV RNA concentrations [7]	X	X	X	X	X	X	X	X	X	X
Plasma for drug resistance monitoring [8]		X	X	X	X	X	X	X	X	X
Pregnancy Test [9]	X							X		
Optional stored serum sample [10]	X	X			X	X	X	X	X	X

[5] A single predose PK sample will be collected at each indicated visit for AL-335(and metabolites), ODV and SMV concentrations for all subjects. In addition, PK samples will be collected at Weeks 3 and 6, 2-4 hours postdose, and at Week 4, 6-8 hours postdose. Subjects in the intensive PK subset will have the following samples collected at the Week 2 visit Predose (within 0.5 hour) and 0.5, 1, 2, 3, 4, 6, 9, and 24 hours postdose.

[6] Blood for routine safety evaluations should be collected in a fasted state.

[7] Plasma for HCV RNA analysis to be collected predose at Day 1.

[8] Plasma collected for HCV RNA resistance monitoring will be collected at the same time as HCV RNA quantification. The Day 1 samples must be collected predose.

[9] A highly sensitive pregnancy test (e.g., urine or plasma) must be conducted immediately (within 4 days) prior to initiating treatment on Day 1 (local results may be used for this eligibility determination)

[10] For additional safety investigations as needed.

* Weekly visit may occur ±1 day from the expected visit date.

Table 6-3. Schedule of Events for a 4-Week Treatment Group

Interval / Assessments	Screen -50 to -1	Day 1	Day 2	Day 3	Week 1*	Week 2*	Week 3*	Week 4*
AL-335+ODV±SMV [1]		< ---------- >						
Obtain informed consent before study procedures	X							
Demographics	X							
Height, Weight, BMI [2]	X							X [2]
Drug Screen	X							
Medical History	X							
Echocardiogram	X (±3 days)							X (±3 days)
Triplicate 12-Lead electrocardiogram	X	X			X	X	X	X
Physical Exam and vital signs [3]	X	X			X	X	X	X
Hepatitis and HIV screen (HBsAg, HBsAB, HBcAb, HCVAb, HIVAb)	X							
Alpha-fetoprotein, glycosylated HbA1C	X							
HCV genotype/subtype	X							
IL28B genotype		X						
Enrollment [4]		**X**						
AE & Conmed Evaluation	X	X	X	X	X	X	X	X

[1] Cohorts 1b, 2 to 16 may or may not include SMV. Dosing frequency will be qd except possibly for ODV which may also be dosed qod.

[2] Weight only collected at Week 4.

[3] Complete Physical Exams, including vital signs (BP, HR, RR, body temperature), are to be done at screening, predose on Day 1, early termination, safety follow-up visits. Symptom directed physical exams and vitals are to be collected as necessary at all other visits. Vital signs will be collected at all visits indicated.

[4] Enrollment may take place up to 4 days before first dose.

Table 6-3. Schedule of Events for a 4-Week Treatment Group

Interval / Assessments	Screen -50 to -1	Day 1	Day 2	Day 3	Week 1*	Week 2*	Week 3*	Week 4*
PK Samples [5]		X			X	X	X	X
Hematology [6]	X	X			X	X		X
Serum Chemistries [6]	X	X			X	X		X
Urinalysis	X	X			X	X		X
ALT/AST [6]	X	X			X	X	X	X
HCV RNA concentrations [7]	X	X	X	X	X	X	X	X
Plasma for drug resistance monitoring [8]		X	X	X	X	X	X	X
Pregnancy Test [9]	X							X
Optional stored serum sample [10]	X	X			X	X	X	X

[5] A single predose PK sample will be collected at each indicated visit for AL-335 (and metabolites), ODV and SMV concentrations for all subjects. In addition, PK samples will be collected at Week 3, 2-4 hours postdose, and at Week 4, 6-8 hours postdose. Subjects in the intensive PK subset will have the following samples collected at the Week 2 visit Predose (within 0.5 hour) and 0.5, 1, 2, 3, 4, 6, 9, and 24 hours postdose.

[6] Blood for routine safety evaluations should be collected in a fasted state.

[7] Plasma for HCV RNA analysis to be collected predose at Day 1, 2 and 3.

[8] Plasma collected for HCV RNA resistance monitoring will be collected at the same time as HCV RNA quantification. The Day 1 samples must be collected predose.

[9] A highly sensitive pregnancy test (e.g., urine or plasma) must be conducted immediately (within 4 days) prior to initiating treatment on Day 1 (local results may be used for this eligibility determination)

[10] For additional safety investigations as needed.

* Weekly visit may occur ±1 day from the expected visit date.

Table 6-4. Schedule of Events for Post-dosing (Safety and Virology) Follow-up Visits (All Treatment Cohorts)

Post-dosing Follow-up							
			Virology Follow-up Visits (After end of Treatment [2] OR After Time of Treatment Failure [if earlier]) [3]				
Assessment	Early Termination (ET) Visit [1]	Safety Follow-up Visit 4 Weeks (±1 week) After the Last Actual Dose of Study Drug	Week 4 (±1 week) [4]	Week 8 (±1 weeks)	Week 12 (±2 weeks)	Week 18 (±2 weeks)	Week 24 (±2 weeks)
Physical Exam [5]	X	X					
Echocardiogram	X	X					
Vital Signs	X	X					
Triplicate 12 Lead ECG	X	X					
Liver Ultrasound (subjects with cirrhosis)							X
Serum Chemistry w/ ALT & AST	X	X					
Hematology	X	X					
Urinalysis	X	X					
HCV RNA concentration	X	X	X	X	X	X	X
Plasma for drug resistance monitoring	X	X	X	X	X	X	X
AE & Conmed Evaluation	X	X	X	X	X	X	X
PK Samples [6]	X	X	X	X	X	X	X

[1] Subjects who prematurely discontinue from their assigned study treatment should return to the clinic as soon as possible for an Early Termination Visit. If the timing of the Early Termination Visit coincides with the Safety Follow up Visit, then assessments for the Early Termination Visit should be conducted.

[2] For subjects with less than lower limit of quantitation (<LLOQ) HCV RNA at actual end of treatment (EOT) (if prematurely discontinued treatment, discontinuation was for reasons other than on-treatment virologic failure (e.g., AE).

[3] See "Definitions" in the beginning of the protocol for definition of on treatment failure. No subject will be followed for more than 24 weeks.

[4] Note: The Week 4 Virology Follow up Visit will coincide with the Safety Follow-up Visit for most subjects and may be replaced by the Safety Follow-up Visit in these cases; it will not coincide for subjects who have relapse or for subjects who discontinue early with <LLOQ HCV RNA.

[5] Complete Physical Exams, including vital signs (BP, HR, RR, body temperature), are to be done at screening, predose on Day 1, early termination, safety follow-up visits. Symptom directed physical exams and vitals are to be collected as necessary at all other visits.

[6] PK sampling will be conducted for ODV at the time of visit.

[7] Heterosexually active women of childbearing potential.

[8] For additional safety investigations as needed.

Pregnancy test[7]	X	X		X	X		X
Optional stored Serum Sample[8]	X	X					

6.2 On-study Evaluations and Procedures

Where multiple procedures are scheduled at the same timepoint(s) relative to dosing, the following order of events should be adhered to, where possible:

- Obtain ECGs first and then vital signs, as close as possible to scheduled times but prior to blood specimen collections.
- All other procedures should be obtained as close as possible to the scheduled time, and may be obtained before or after blood specimen collection

6.2.1 Pharmacokinetic Blood Sampling

Blood samples for PK analysis will be collected at the scheduled times via an indwelling catheter and/or direct venipuncture. Saline or heparin flushes may be used to maintain viability of indwelling catheters. Additional information may be found in the Pharmacokinetic Sample Processing Manual.

The total volume of blood required for the intensive PK profile is up to 90 mL per subject, and approximately 20 mL for all other subjects

Blood samples will be assessed for plasma concentrations of ALS-022335, ALS-022399 and ALS-022227, SMV, and ODV using validated liquid chromatography–tandem mass spectrometry methods. In addition, plasma PK samples may be stored for future analysis of the protein-binding and/or metabolite profile.

6.2.1.1 AL-335

Details on the collection, processing, storage of AL-335 PK samples are provided in the Laboratory Manual.

Blood samples will be collected to determine the concentration of ALS-022335, ALS-022399, ALS-022227 at times specified in the Schedule of Events, Table 6-1 through Table 6-4.

6.2.1.2 Odalasvir

Details on the collection, processing, storage of ODV PK samples are provided in the Laboratory Manual.

Blood samples will be collected to determine the concentration of ODV at times specified in the Schedule of Events, Table 6-1 through Table 6-4.

6.2.1.3 SMV

Details on the collection, processing, storage of SMV PK samples are provided in the Laboratory Manual.

Blood samples will be collected to determine the concentration of SMV at times specified in the Schedule of Events, Table 6-1 through Table 6-4.

For all samples, all efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Deviations will be defined in the study manual. The exact time of sample collection will be noted on the source document and the data collection tool.

PK samples may also be collected on an ad hoc basis as a safety assessment in the event that a safety event arises, for which an understanding of drug exposure is clinically important.

6.2.2 Laboratory Evaluations

Laboratory evaluations will be performed both locally, to enable time sensitive safety-driven decisions, and centrally, for eligibility determination (screening) and the final data analysis. The local laboratory result on Day 1 may be used to confirm continued eligibility.

The central interpretation of laboratories should also be used for clinical decision making (e.g., need for additional workup) unless the local reading is considered sufficiently concerning that it is not appropriate to delay decision making until the central reading can be performed.

In subjects that provide additional informed consent, an optional serum sample will be collected. This sample may be utilized as a back-up specimen for safety assessments. This sample may also be utilized to explore the impact patient characteristics and potential biomarkers have on treatment outcomes.

6.2.3 HCV RNA Evaluations

Blood samples for the determination of HCV RNA levels will be taken at all timepoints, processed in real time (centrally) and closely monitored by the Sponsor. The procedures for sample collection, processing and storage will be provided in the laboratory manual.

Plasma HCV RNA levels will be determined using an in vitro nucleic acid amplification test for quantification of HCV RNA in human plasma.

Results will be communicated to the Investigators throughout the study.

In case HCV RNA is detectable after previous undetectability, the results should be confirmed by an HCV RNA retest, which should be scheduled by the investigator as soon as possible (preferably within 2 weeks) after the HCV RNA results become available. This might require an unscheduled visit. At the time of the retest sample for HCV RNA, a sample for HCV resistance evaluation will also be collected.

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

6.2.4 HCV Resistance Evaluation

Sequencing of the HCV NS3/4A, NS5A and NS5B regions will be performed to identify pre-existing sequence polymorphisms and characterize emerging HCV viral variants. Blood samples for HCV resistance evaluation will be taken at all timepoints to identify pre-existing sequence polymorphisms and characterize the potential of emergence of viral resistance to AL-335, ODV and SMV.

The NS3/4A, NS5A and NS5B regions will be sequenced pre-treatment (from a baseline sample) by default in all subjects and post-baseline only in subjects not achieving SVR. Additional sequencing of samples may be requested upon review 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.

6.2.5 12-Lead Electrocardiograms

The investigator will be responsible for evaluating the results and determining if any findings are of clinical significance. Throughout the study, triplicate ECGs will be obtained in a semi-recumbent or recumbent position at the time points specified in Schedule of Events (Table 6-1 through Table 6-4). The subject should be at rest and in a (semi)recumbant position for at least 5 minutes before ECG recordings and remain resting and in that position during the recording. Triplicate ECGs will be performed 1-5 minutes apart and may be repeated at the investigator's discretion to account for erroneous readings. Sequential ECGs will be collected until 3 useful recordings are obtained without artifact.

The average of the 3 readings' ECG intervals will be used to determine if the subject meets the entry criteria or fulfills criteria which would require study drug(s) discontinuation or additional workup.

All ECG recordings must be performed using a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements. Each ECG will be assessed by a central reader.

The centrally read screening electrocardiogram results should be used for eligibility determination. The local reading of the ECG on Day 1 may be used to confirm continued eligibility. The central interpretation of electrocardiograms should also be used for clinical decision making (e.g., need for additional workup) unless the local reading is considered sufficiently concerning that it is not appropriate to delay decision making until the central reading can be performed.

Digital ECG recording is required. A duplicate for each ECG tracing will be obtained. One copy will be sent electronically for assessment by the central reader and the other copy kept at the study center.

For safety monitoring purposes, the investigator must review, sign and date all ECG tracings. Paper copies will be kept at the study center with the subject's clinical file as part of the permanent record. The ECG intervals (HR, PR, QRS, QT, QTcB, QTcF), information on T- (normal or abnormal) and U-waves (absent/normal or abnormal), any clinically significant ECG abnormalities, and remarks will be recorded on the CRF. All ECGs will be compared over time as an assessment of safety by a central reader.

6.2.6 Echocardiograms

Echocardiograms will be performed at regular intervals (Section 6.1, Schedule of Events) and according to a standard protocol (see Study Manual). There will be a ±3-day visit window for these assessments except for screening visit. A variety of echocardiographic parameters, including ejection fraction and diastolic parameters will be quantitated and compared over time as an assessment of safety by a central reader.

The centrally read echocardiogram results should be used for eligibility determination. The central interpretation of echocardiograms should also be used for clinical decision making (e.g., need for additional workup) unless the local reading is considered sufficiently concerning that it is not appropriate to delay decision making until the central reading can be performed.

6.2.7 Vital Signs

Vital signs (oral or body temperature, RR, automated supine BP and HR) will be obtained in a semi-recumbent or recumbent position after 5 minutes of rest. Blood draws will take precedence over vital signs in the event that the 2 procedures need to be conducted at the same time. In this case, vital signs should be obtained as close to the scheduled time as possible, after ECG assessments and prior to blood collections.

6.2.8 Physical Examinations

Complete Physical Exams, including vital signs (BP, HR, RR, body temperature), are to be done at screening, predose on Day 1, early termination, safety follow-up visits. A brief symptom directed examination will be conducted at all other timepoints as indicated in the Schedule of Events. BMI will be calculated by clinic staff at the Screening visit using the following formula:

$$\text{BMI} = \text{weight in kg} \div (\text{height in meters})^2$$

6.2.9 Contraception

Contraception requirements from screening through completion of the study are defined in the Inclusion criteria (see Sections 4.2 and 4.3).

7.0 SAFETY MONITORING AND REPORTING

7.1 Definitions

7.1.1 Pretreatment Events

A pretreatment event is any event that meets the criteria for an AE/SAE and occurs after the subject signs the ICF but before receiving the first administration of study drug.

7.1.2 Adverse Events

An AE is any event, side effect, or untoward medical occurrence in a subject enrolled in a clinical trial whether or not it is considered to have a causal relationship to the study drug. An AE can therefore be any unfavorable and unintended sign, symptom, laboratory finding outside of normal range with associated clinical symptoms or suspected latent clinical symptoms in the opinion of the investigator, physical examination finding, or disease temporally associated with

the use of the study drug, whether or not the event is considered related to the study drug. 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.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (e.g., surgery was performed earlier than planned).

7.1.3 Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death: This includes deaths that appear to be completely unrelated to study medication (e.g., a car accident).
- Is a life-threatening event: An event that places the subject at immediate 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 prolonged hospitalization of an existing hospitalization.
- Results in permanent or prolonged (at least 28 days in duration) disability or incapacity.
- Is a congenital anomaly or birth defect in the offspring of a study subject.
- Medically important event: An event that may not be immediately life-threatening, or result in death or hospitalization, or require intervention to prevent one of the outcomes listed above, but is considered medically significant for other reasons. An opportunistic or otherwise unusual infection for the investigator's practice, such as tuberculosis, will be considered medically significant.

The term severe is used to describe the intensity of a specific event (as in mild, moderate, or severe); the event itself, however, may be of minor medical significance (such as severe headache). This is not the same as serious, which is based on outcome of the event, as described above. Seriousness, not intensity, serves as a guide for defining regulatory reporting obligations.

7.2 Documenting and Reporting of AEs (including SAEs)

Adverse events will be evaluated and documented using the grading scales contained in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (November 2014) and shown in Appendix F.

7.2.1 Documenting and Reporting Pretreatment Events

For enrolled subjects, record all pretreatment AEs that occur after the subject signs the ICF but before the first study drug administration on the AE CRF and Clinical Trials SAE Form (if applicable). The AE CRF and SAE form will indicate that the event occurred prior to the first dose of study drug.

7.2.2 Documenting and Reporting AEs

Record all AEs that occur from Day 1 (from start of study medication administration) to the follow-up visit, regardless of the intensity, seriousness, or relationship to study drug, on the AE CRF, for all enrolled subject. Subjects who do not enroll (i.e., screen failures), collect AEs until the time of screen failure.

Once an event has resolved, any recurrence will be reported as a new event with a corresponding grade.

Clinically significant changes in objective findings (e.g., laboratory, ECG, physical examination) should be considered AEs only if they meet the following criteria:

- Associated with accompanying symptoms; and/or,
- Require medical/surgical intervention; and/or,
- Lead to discontinuation from the study; and/or
- Lead to significant additional concomitant drug treatment, or other therapy; and/or,
- Lead to any of the outcomes included in the definition of an SAE.

Whenever possible, the etiology of the abnormal findings (rather than the abnormal finding(s) itself) should be documented as the AE. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated. An AE includes the following:

- Pre-existing event that increases in frequency or intensity.
- Condition detected or diagnosed during the study period, even though it may have been present, in retrospect, prior to the first dose of study drug.
- Laboratory abnormalities outside of normal limits and requiring therapeutic intervention.
- An overdose of the study drug without any signs or symptoms will be considered an AE. A calculated dose that exceeds its correct dose by 10% or more and is administered to the subject will be considered an overdose and documented as an AE.

The following events **will not** be identified as AEs in this study:

- Progression or exacerbation of the subject's underlying disease. However, clinical sequelae that result from disease progression, such as pleural effusion or small bowel obstruction, are reportable as AEs.
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, etc); however, the condition (the "triggering event") that leads to the procedure may be an AE.
- Pre-existing conditions present or detected prior to the first dose of study drug that do not worsen.

7.2.3 Assigning Attribution of AEs

The investigator **must** attempt to determine the cause of each event. To ensure consistency of AE/SAE causality assessments, investigators should apply the following guideline:

Related:
There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event re-appeared on re-exposure to the investigational study drug.

Possibly Related:
There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.

Unlikely Related:
The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.

Not Related:
The event is related to an etiology other than the investigational study drug (the alternative etiology must be documented in the study subject's medical record).

7.2.4 Classifying Action Taken With Study Drug

Classification	Definition
Dose Not Changed	Study Drug dose not changed in response to the AE
Drug Interrupted	Study drug administration interrupted in response to an AE
Drug Withdrawn	Study drug administration permanently discontinued in response to an AE
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt or withdraw treatment is possible.

7.2.5 Classifying AE Outcome

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms
Recovered/Resolved with sequelae	Resolution of an AE with residual signs or symptoms
Not Recovered/ Not resolved (continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. "Fatal" should be used when death is at least possibly related to the adverse event.
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow up)

7.2.6 Documenting and Reporting Serious Pretreatment Events and SAEs

All SAEs that occur after obtaining informed consent through the Follow–up visit, regardless of causality, must be reported by the investigator to the Sponsor designee for SAE reporting. See study manual for reporting specifics. In addition, all SAEs, including those that result in death, that occur after the Completion Visit and that are considered related to study drug(s) must be reported to Sponsor's designee within 24 hours.

SAEs will be recorded on the Clinical Trials SAE Form using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for severity, relationship to the investigational study drug(s) and possible etiologies. On the Clinical Trials SAE Form, relationship to study drug(s) will be assessed only as related or not related, and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report to Sponsor's designee the outcome of the event using the SAE Form.

The investigator is responsible for notifying the Sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The SAE Form should be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available, to ensure timely reporting to Health Authorities.

The SAE Form should be faxed to Sponsor's designee using the fax cover sheet provided.

Alios BioPharma or its designees, as study Sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, and participating investigators, in accordance with International Conference on Harmonisation (ICH) Guidelines, and/or local regulatory requirements, as applicable.

7.2.7 Documenting and Reporting of Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study treatment and for 6 months after the last dose of study drug/s.

If a subject or the female partner of a male subject becomes pregnant while participating in the study, study treatment must be permanently discontinued immediately. The investigator must notify the Sponsor's Medical Monitor and CRO within 1 business day of the sites' knowledge of the subject's (or partner's) pregnancy, by utilizing the Pregnancy Initial Report Form. The subject or partner will be followed until end of pregnancy and the infant will be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

7.3 Follow-up of AEs and SAEs

Follow all AEs (serious and non-serious) until resolution or otherwise explained, the subject dies, the event stabilizes and is not expected to further resolve, or when alternative therapy is instituted, whichever occurs first. If alternative therapy is instituted, it should be documented.

Alios BioPharma may request that the investigator perform or arrange for supplemental measurements or evaluations to further clarify the nature of the event.

7.4 Sponsor's Review of AEs and SAEs

Alios BioPharma will maintain an ongoing review of all AEs and SAEs.

7.5 Special Safety Considerations

7.5.1 Creatine Kinase

Because nucleosides, as a class, have a known risk of mitochondrial toxicity, which is often manifest 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.

In the event a subject develops clinical signs suggestive of muscle injury (e.g., proximal weakness, myalgias), a thorough workup (e.g., assessment of CK, CK-MB fraction (or, alternatively, troponin), aldolase, myoglobin, calcium, phosphate, creatinine, and urinalysis) for muscle injury should be performed.

If a study subject's CK is found to be elevated >3×ULN (without a concomitant proportionate CK-MB or troponin elevation), the following stopping criteria for CK elevations should be applied (Pasternak et al. 2002):

In subjects (whether symptomatic or asymptomatic) without a clinical history to suggest etiology of CK elevation (e.g., recent exercise or exposure to medication with known risk of myopathy):

- If CK is ≥20× ULN, immediately re-draw and repeat the test. If the repeat remains ≥20× ULN, discontinue study medication
- If CK is ≥3 – <20×ULN:
    - Continue study medication. Assess CK, CK-MB/troponin every ~72 hours (follow-up assessments) until the CK has normalized (follow-up assessments)
    - If any follow-up CK assessment is ≥20× ULN, discontinue study medication
    - if the 3rd follow-up CK assessment (i.e., ~9 days after CK elevation was first recognized) is ≥ the prior follow-up CK assessment, discontinue study medication

In subjects with a clinical history suggestive of a non-study drug-related etiology for a CK elevation ≥3×ULN (e.g., recent exercise or exposure to medication with known risk of myopathy):

- Study medication may be continued. These patients should immediately discontinue the putative cause of their CK elevation and the CK and CK-MB/troponin should be assessed every ~72 hours (=follow-up assessment).
- If initial CK is ≥3- <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/troponin every ~72 hours. If the 3rd follow-up CK assessment (i.e., ~9 days after CK elevation was first recognized) is ≥ the prior follow-up CK assessment, discontinue study medication.

For any study subject with a treatment-emergent CK >1.5- <3× ULN, consider repeat CK, CK-MB/troponin in ~72 hours and continue testing until CK decreases

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

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

In all cases where a CK >10× ULN or discontinuation of study drug is planned due to suspected muscle injury, the Sponsor Medical Monitor MUST be notified within 24 hours so that the clinical case and workup and treatment strategy can be discussed.

7.5.2 Cardiotoxicity

A theoretical risk of nucleosides is mitochondrial toxicity that can manifest as cardiac toxicity/congestive heart failure. Surveillance for this theoretical risk will be done in this study via assessments of AEs, ECGs and echocardiograms, which will be obtained at specified timepoints during the treatment period in this study.

In order to effectively monitor for potential treatment-related cardiotoxicity during the study, subjects presenting at screening must have:

- ECG PR interval must be <200 msec and there must be no evidence of any conduction blocks.
- echocardiogram ejection fraction (EF) must be ≥55%.

During the treatment period, emergence of or changes in symptoms or clinically significant findings in ECG may trigger the following stopping criteria:

If a first degree AV block is diagnosed and:

- The PR interval is >200 msec but ≤240 msec, study drugs can be continued. Close monitoring with weekly ECG is recommended.
- 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. Based on this assessment, the study drugs may or may not be continued. Close monitoring with weekly ECG is recommended.

- 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. The Investigator and Sponsor Medical Monitor must determine whether or not continued dosing with AL-335 and SMV is acceptable for subjects that discontinue ODV.
- If a second degree or higher AV block is diagnosed (confirmed by a repeat triplicate analysis at least 30 minutes after the initial assessment and irrespective of presence or absence of clinical symptoms), ODV must be discontinued. The Investigator and Sponsor Medical Monitor must determine whether or not continued dosing with AL-335 and SMV is acceptable for subjects that discontinue ODV.

All study medications must be discontinued:

- In asymptomatic patients with no clinical evidence of congestive heart failure:
  - If the absolute decline from baseline in EF is >10% AND the post-baseline EF is <50%; e.g., 60% →49%)

NOTE: For asymptomatic subjects without clinical evidence of heart failure, but with an apparent decline in EF of >10%, an urgent repeat echocardiogram may be performed to confirm the finding. If confirmed and <50%, all study drugs should be discontinued as described above. If the confirmatory EF is ≤10%, the Investigator and Medical Monitor should perform a cardiology assessment (see below) and, based on the subject's overall clinical picture, decide whether or not to discontinue study drug.

  - If the absolute decline from baseline in EF is >5% and ≤10%, an urgent unscheduled visit must occur for the assessment of the subject's clinical status, including symptoms, physical exam, and other clinical parameters. This assessment should occur before deciding whether to stop or continue study drugs.

- In symptomatic subjects (e.g., dyspnea, orthopnea) or subjects with signs of congestive heart failure (e.g., S3 gallop, pedal edema, pulmonary edema):
  - If the absolute decline from baseline in EF is ≥5% (e.g., 61%→54%)
  - The Investigator and Sponsor Medical Monitor may also deem it necessary to discontinue study drug in symptomatic subjects with an absolute decline from baseline in EF of <5%

- In asymptomatic or symptomatic subjects with clinical evidence of heart failure:
  - If absolute decrease in EF from screening is >10%, these subjects must undergo mandatory assessment (see below) and have an urgent cardiology referral; the EF decrease must be reported to the Medical Monitor within 24 hours so that the clinical case and workup and treatment strategy can be discussed.

Subjects with an absolute decrease from screening of >5% to ≤10% in LVEF must have an urgent unscheduled visit for further assessment as soon as possible.

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

- Cardiopulmonary review of systems and physical examination,
- Troponin I assessment - (serial assessments may be indicated)
- BNP or Pro-BNP (serial assessments may be indicated)
- 12-lead ECG and
- Additional echocardiography (at study approved facility) – if clinically indicated, at a frequency determined by the Investigator's judgment.

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

7.5.3 Prolonged QTc (i.e., >500 msec or change from baseline of >60 msec)

If a post-baseline QTc is found to be prolonged to >500 msec or if there is a change from baseline of >60 msec in repeat ECG assessments (e.g., triplicate ECGs) and this change is deemed clinically significant, all study drugs should be discontinued. Additional cardiac workup may be performed at the discretion of the Investigator. Any subject with prolonged QTc should be advised to discontinue and avoid any medications known to prolong QTc. In addition, serial ECGs (approximately weekly) should be assessed until the subject's QTc has returned to baseline.

7.5.4 Renal Safety Monitoring

Renal safety will be monitored by evaluating urine dipstick leukocyte esterase, serum creatinine levels, eGFR and serum chemistry results. The investigator should closely monitor for clinically relevant changes in serum creatinine and eGFR. In case renal complications develop, subjects must be treated as clinically appropriate. Dosing may continue if the renal complication is considered not to be related to study drug in the opinion of the investigator.

For eGFR monitoring, the following guidance should be followed:

- If the eGFR value is <30 mL/min/1.73m^2, 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/1.73m^2, all study drugs must be interrupted and renal function should be followed as clinically appropriate.

Recommencement of treatment should be discussed with the Sponsor on a case-by-case basis.

7.6 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. 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 7-1.

Discontinuation of SMV should be considered if a photosensitivity reaction occurs and subjects should be monitored until the reaction has resolved. If a decision is made to continue SMV in the setting of a photosensitivity reaction, expert consultation is advised.

Table 7-1. Guidelines for Subjects Developing Rash Grade 1 to Grade 4

WHO Grade	Rash Definition	Investigator Action
Grade 1 Rash (with or without pruritus) [a]	Erythema	May continue intake of study drugs at the investigator's discretion.
Grade 2 Rash (with or without pruritus) [b]	diffuse, maculopapular rash, OR dry desquamation	May continue intake of study drugs at the investigator's discretion.
Grade 3 Rash	• 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 $\times 10^3/\mu L$	Permanently discontinue the intake of SMV. May continue intake of ODV and AL-335 at the investigator's discretion. No rechallenge is allowed.
Grade 4 Rash	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.

[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

[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.

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

When safety blood samples are drawn as per the rash management guidelines, these should be processed by the local laboratory; a separate blood sample should also be sent for central laboratory confirmation. The following parameters will need to be tested: AST, ALT, sedimentation rate, complete blood cell count (including hemoglobin, hematocrit, red blood cell count, white blood cell 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 (e.g., cetirizine, levocetirizine) and/or topical corticosteroids may provide symptomatic relief but effectiveness of these measures has not been established. If systemic corticosteroids for longer than 24 hours are required for treatment of rash, the study drugs need to be permanently discontinued. If the rash is considered to be most likely due to concomitant illness or non-study drugs, standard management, including discontinuation of the likely causative agent, should be undertaken.

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

The following grades are based on the WHO Toxicity Grading Scale.

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 Grades 3 to 4 rash, respectively.

Grade 2 Rash (with or without pruritus)

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

- Subjects may continue the intake of study drugs (at the investigator's discretion).
- An unscheduled visit for initial rash evaluation is required as soon as possible after the subject contacts the investigator to report the AE. If a visit is not possible, telephone contact with the subject should take place to collect information and to give advice on the necessary measures to be taken.
- Assessment of safety blood samples by the local laboratory is recommended. The values of the local laboratory assessments need to be transcribed in the eCRF by the study-site personnel.
- Referral to a dermatologist is optional but, when done, should occur preferably within 24 hours after the onset of the rash. A copy of the dermatologist's report should be made anonymous and will be collected by the monitor.

Unscheduled visits will also be performed after the initial rash assessment at the investigator's discretion for appropriate follow up until resolution of the rash. At these visits, safety blood samples must be taken. 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 sickness-like reaction

Subjects will permanently discontinue SMV and may continue ODV and AL-335 (monotherapy with any of the study drugs is not allowed). No rechallenge is allowed.

A Grade 4 rash is defined as:

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

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

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

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

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

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

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

7.7 Acute Allergic Reaction

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

Management of acute allergic reactions will take into account the protocol-defined procedures outlined in Table 7-2.

Table 7-2. 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.

7.8 Liver Function Tests

Liver chemistry management criteria have been designed to ensure subject safety. When subjects meet the liver chemistry threshold criteria, the subject's clinical case should be carefully reviewed with the medical monitor, additional testing performed, and the subject monitored until liver chemistries resolve, stabilize, or return to baseline values.

In situations requiring additional liver chemistry monitoring, every attempt should be made to obtain the following after discussion with the medical monitor:

Viral hepatitis serology including:

- Hepatitis A immunoglobulin M (IgM) antibody
- HBsAg and hepatitis B core antigen IgM antibody
- HCV RNA
- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
- Hepatitis E IgM antibody

- Blood samples for study medication PK analysis. If study treatment is discontinued, blood samples should be obtained within 2 days of the last dose of study drug. Record the date/time of the PK blood sample draw and the date/time of the last dose of the study drug before blood sample draw in the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do

not obtain the PK samples. Instructions for sample handling and shipping are in the Laboratory Manual.

- Serum creatine phosphokinase and lactate dehydrogenase
- If total bilirubin ≥ 2× ULN, fractionated bilirubin
- Complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the CRF
- Record use of concomitant medications, acetaminophen, herbal remedies, other OTC medications, or putative hepatotoxins, on the CRF
- Record alcohol use on the liver event alcohol intake page of the CRF

The following are required for subjects who meet the ALT and bilirubin management criteria but are optional for other abnormal liver chemistries and should be discussed with the medical monitor:

- Antinuclear antibody, antismooth muscle antibody, and type 1 anti-liver/kidney microsomal antibodies
- Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, detectable by high-performance liquid chromatography assay more than 1 week following acetaminophen use) (James et al. 2009)
- Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease

7.9 ALT, AST, 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 closely monitored, with unscheduled study visits if needed. Increases in bilirubin (both direct and indirect) have been observed during the first weeks of SMV therapy. These bilirubin elevations are caused by a benign competitive inhibition of biliary transporter systems in hepatocytes. Bilirubin elevations following initiation of SMV therapy are typically not associated with increases in ALT or AST levels and rapidly resolve after completion of SMV treatment. Bilirubin elevations have been observed to a much lesser extent with direct-acting antiviral regimens where SMV is administered without RBV compared to when it is administered with RBV.[16]

Management of treatment-emergent AST, ALT and/or bilirubin elevations will take into account the protocol-defined procedures outlined in Table 7-3, Table 7-4, and Table 7-5.

Table 7-3. 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

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× 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 7-4).

In case of a Grade 4 bilirubin value, subjects should have a confirmatory measurement within 72 hours after receipt of the results. If the Grade 4 value is confirmed but not considered a sign of worsening liver disease, or if there is an identifiable cause for the value (e.g., hereditary hyperbilirubinemia [Gilbert's syndrome] or concomitant medication associated event), subjects may continue the study drugs or have SMV discontinued while ODV and AL-335 can be continued at the investigator's discretion (Table 7-5). Subjects who continue the study drugs should be carefully evaluated and close follow up is recommended to monitor for progressive increase in bilirubin levels. If the Grade 4 value is confirmed and is considered a sign of worsening liver disease, or if there is no identifiable explanation for the confirmed value, all study drugs should be discontinued.

For concurrent Grade 4 ALT and/or AST elevations >2× the baseline value and Grade 4 bilirubin values, subjects should have a confirmatory measurement within 72 hours after receipt of the results. In case of confirmed Grade 4 elevations, the study drugs should be discontinued.

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

Table 7-4. Guidelines for Subjects Developing ALT and/or AST Elevations

WHO Toxicity Grade	Ranges	Investigator Action
Grade 1	≥1.25 to ≤2.5× ULN	May continue intake of study drugs at the investigator's discretion. Monitor for progressive increase in ALT and/or AST levels
Grade 2	>2.5 to ≤5.0× ULN	May continue intake of study drugs at the investigator's discretion. Monitor for progressive increase in ALT and/or AST levels
Grade 3	>5.0 to ≤10.0× ULN	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. May continue study drugs at the investigator's discretion (upon agreement with the Sponsor) if value is ≤2× 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.
Grade 4	>10.0× ULN	If the Grade 4 ALT and/or AST value is >2× 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.

NOTE:

Any significant ALT flare, defined as

1) ALT of >2x ULN AND >2X the lowest value during the study

OR

2) any treatment emergent grade 3 ALT elevation (>5 x ULN)

will trigger a thorough clinical work-up of the case by the investigator. This evaluation should include the assessment of serum HBV-DNA (mandatory in subjects that are anti-HBc ab positive at screening or baseline). If HBV reactivation is confirmed, then appropriate treatment for HBV should be started if clinically appropriate.

Table 7-5. Guidelines for Subjects Developing Bilirubin Elevations

WHO Toxicity Grade	Ranges	Investigator Action
Grade 1	≥1.1 to ≤1.5× ULN	May continue intake of study drugs at the investigator's discretion. Monitor for progressive increase in bilirubin levels.
Grade 2	>1.5 to ≤2.5× ULN	May continue intake of study drugs at the investigator's discretion. Monitor for progressive increase in bilirubin levels.
Grade 3	>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 and: • Not considered a sign of worsening liver disease, or if there is an identifiable cause [a] for the confirmed value, subjects may continue study drugs or have SMV discontinued while ODV and AL-335 can be continued at the investigator's discretion. [b] • Considered a sign of worsening liver disease, or if there is no identifiable explanation for the confirmed value, all study drugs should be discontinued. Monitor for progressive increase in bilirubin levels

a. For example, hereditary hyperbilirubinemia (Gilbert's syndrome) or concomitant medication associated event.
b. Monotherapy with any of the study drugs is not allowed.

8.0 STUDY VARIABLES AND MEASUREMENTS

8.1 Safety Variables/Measurements

Safety evaluation will include AEs and SAEs, vital signs, laboratory tests (including hematology and serum chemistries), ECG, echocardiograms, physical examination, urinalysis, and pregnancy tests.

8.1.1 Adverse Events

Adverse events, including pretreatment events, will be recorded from the time of consent through the SVR24 visit. All AEs/SAEs will be coded using the *Medical Dictionary for Regulatory Activities (MedDRA)*.

8.1.2 Clinical Laboratory Measurements

Clinical laboratory variables, including hematology, serum chemistries, urinalysis, and pregnancy testing, will be assessed at screening. Hematology, serum chemistries, and pregnancy testing will be evaluated periodically during the study as indicated in this protocol. Local labs will be used for real time clinical decision making, while central labs will be used for purposes of the clinical database.

8.1.3 Prior and Concomitant Medications

Use of all medications and supportive therapy from within 30 days of the screening visit through study completion will be recorded. All concomitant medications will be mapped using the WHO Drug Dictionary.

8.2 Efficacy Variables/Measurements

HCV RNA will be measured in all subjects (Section 6.2.3).

The key efficacy variables include the proportion of subjects who achieve SVR demonstrated by sustaining HCV RNA <LLOQ 4, 8, 12, 18 and 24 weeks after the end of treatment (SVR4, SVR8, SVR12, SVR18 and SVR24), regardless of whether or not the subject completed the assigned treatment regimen.

The results will be presented by treatment group by means of descriptive statistics.

The SVR rates will also be presented by subgroups defined by baseline characteristics such as HCV genotype, prior HCV treatment, and IL-28B genotype status.

Additional efficacy variables to be analyzed include:

- The proportion of subjects who have relapse (i.e., who had <LLOQ HCV RNA at actual end of treatment (EOT) followed by ≥LLOQ HCV RNA after planned EOT)
- The proportion of subjects who achieve undetectable HCV RNA <LLOQ (undetectable) at Weeks 2, 4, 6, and 8 after the first dose of study drug
- Time to achieve HCV RNA <LLOQ and <LLOQ undetectable
- The proportion of subjects who have on treatment failure
- The proportion of subjects who achieve SVR12 by IL-28B genotype (CC or non-CC)

8.2.1 Virologic Response

Virologic response is quantitative HCV RNA concentration <LLOQ at any timepoint post-first dose of study drug. An SVR is HCV RNA <LLOQ at Weeks 4, 8, 12, 18 or 24 after cessation of study treatment.

8.2.2 On-Treatment Failure

Subjects who did not achieve SVR12 and with confirmed HCV RNA ≥LLOQ at the actual end of study drug treatment. Includes subjects:

- With viral breakthrough, defined as a confirmed increase of >1 $\log_{10}$ in HCV RNA from nadir, or confirmed HCV RNA of >100 IU/mL in subjects whose HCV RNA had previously been <LLOQ while on treatment.
- With inadequate virologic response, defined as <1 $\log_{10}$ decline from baseline in HCV RNA after 4 weeks of treatment

- Who do not experience viral breakthrough or inadequate virologic response and have confirmed HCV RNA ≥LLOQ at the actual end of study drug treatment (e.g., completed study drug treatment, discontinued due to adverse events, withdrawal of consent).

8.2.3 Relapse

Subjects who achieved HCV RNA <LLOQ at the actual end of study drug treatment and developed HCV RNA ≥LLOQ during post-treatment follow up.

8.3 Viral Resistance

Blood samples will be collected from subjects to identify pre-existing sequence polymorphisms and characterize the potential of emergence of viral resistance to AL-335, ODV and SMV (Section 6.2.4).

8.4 PK Measurements

Blood samples will be collected from all subjects at specified times throughout the study for the determination of PK parameters for AL-335 and its metabolites, SMV, and ODV (time points specified in Table 6-1 through Table 6-4).

Population PK parameters will be estimated by using non-linear mixed effects modeling. In the PK substudy, PK parameters will be estimated using standard non-compartmental methods.

All calculations will use the actual times recorded on the CRF. AL-335, SMV, and ODV plasma concentrations and computed PK parameters will be listed by subject and summarized by treatment group (mean, geometric mean, standard deviation, coefficient of variation, minimum, maximum, number of observations), as appropriate. Individual and mean (by time) concentrations versus time will be plotted by treatment group on both linear and natural logarithm scales.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Considerations

Continuous data will be summarized by descriptive statistics, including number of subjects, mean, standard deviation, median, and range. Categorical data will be summarized by the number and percentage of subjects. A detailed analysis plan for the analysis of safety data, PK data, HCV RNA data, and viral sequencing data will be presented in a statistical/virological analysis plan(s) (SAP) before the database is locked for final analysis. An interim data review may be conducted which will be documented in the analysis plan.

9.2 Study Endpoints

9.2.1 Primary Endpoint

- Safety data including but not limited to tabulation of AEs, physical exam, vital signs, 12-lead ECGs, echocardiogram, and clinical laboratory results (including chemistry, hematology, and urine).

9.2.2 Secondary Endpoints

- The proportion of subjects who have an SVR (i.e., HCV RNA concentration <LLOQ (<15 IU/mL) at 4, 8, 12, 18, 24 weeks after the actual end of study treatment
- PK parameters for AL-335 (and metabolites), ODV and SMV in plasma.
- The proportion of subjects who have virologic relapse during follow up
- The proportion of subjects who have on-treatment failure while receiving study medication
- Viral kinetics, as determined at different timepoints during treatment by the proportion of subjects who achieve
    - HCV RNA <LLOQ Undetectable
    - HCV RNA <LLOQ
- Time to achieve undetectable HCV RNA and <LLOQ HCV RNA
- The amino acid sequence of the NS5A, NS5B and NS3/4A proteins at baseline and post-baseline in subjects who fail treatment.
- Effect of various baseline and host disease-related characteristics on treatment outcome

9.3 Determination of Sample Size

Up to 320 subjects with GT1, GT2 and GT3 CHC will be enrolled. Since there is no formal statistical hypothesis testing, no formal sample size calculation has been performed.

With a total sample size of 320 subjects, the probability to observe an AE with an incidence of 1% is 96%. The probability to observe an AE with an incidence of 0.1%, 0.5% and 0.8% is 27%, 80%, and 92%respectively.

A sample size of 20 evaluable subjects per arm is considered adequate for estimation of PK parameters for each individual compound in the combination regimen. With this sample size, the point estimate of the AUC geometric mean is anticipated to fall within 74.2% and 134.8% of the true value with 90% confidence, assuming an intersubject standard deviation of 0.77 with respect to steady-state log-transformed $AUC_{0\text{-}24h}$.

Further, with an expected SVR rate of 90%, and 20 subjects per arm, the corresponding 95%, 2-sided confidence interval (CI) is 68.3% to 98.8%. With 95% SVR, the corresponding 95% CI ranges from 75.1% to 99.9%.

Therefore, a total sample size of up to 320 subjects is considered sufficient to explore the safety, pharmacokinetics, and efficacy of the study regimen.

10.0 STATISTICAL METHODS

10.1 Study Population

10.1.1 Subject Disposition

An accounting of all subjects over the course of the study will be reported. Enrollment, study drug administration, subject completion, premature discontinuation, and major protocol violations will be tabulated and summarized.

10.1.2 Replacement of Subjects

There will be no replacement of subjects discontinued prematurely for safety reasons.

10.1.3 Procedures for Handling Missing, Unused, or Spurious Data

Strategies for handling missing, unused, or spurious data will be specified in the SAP.

10.2 Analysis Populations

10.2.1 Safety and Efficacy Populations

All subjects enrolled into the study who have received at least one dose of any study drug, whether prematurely withdrawn from the study or not, will be included in the safety/ efficacy population.

10.2.2 Pharmacokinetic Population

Subjects will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

10.2.3 Per Protocol Population

A per protocol analysis including all subjects enrolled and adherent to the protocol will be performed for certain efficacy analyses (see Statistical Analysis Plan).

10.3 Demographics and Baseline Characteristics

Demographic data (age, sex, ethnicity, body weight) and baseline disease characteristics will be tabulated and summarized and presented in data listings.

10.4 Safety Analysis

10.4.1 Adverse Events

The MedDRA will be used to map the AE/SAE verbatim terms to specific system organ classes (SOC) and preferred terms. Adverse events and SAEs will be summarized in summary tables and tabulated in by-subject listings by SOC and preferred term by treatment day. Incidence rates will be presented.

10.4.2 Vital Signs, ECG, Physical Examination, and Laboratory Assessments

Vital signs will be summarized and tabulated by treatment day. The proportion of subjects with abnormal findings based on physical examinations over time will be summarized. Laboratory

values will be graded and summarized based on DAIDS, November 2014. Number and percentage of subjects with Grades 3 and 4 laboratory abnormalities will be tabulated.

In the event a safety signal is detected, the PK/pharmacodynamic relationship between study drug(s) and various safety parameters including ECG changes, vital signs, and relevant laboratory parameters will be evaluated.

10.4.3 Concomitant Medications

All reported concomitant medications will be mapped using the WHO Drug Dictionary. Concomitant medications will be tabulated in summary tables and by-subject listings.

10.5 Pharmacokinetic Analysis

Samples at a single timepoint prior to dosing will be obtained at all routine study visits while subjects are receiving study medication. In addition, for a subgroup of up to 250 subjects, additional samples will be obtained over a 24-hour period at the Week 2 assessment.

The PK parameters for ALS-022335, ALS-022399, ALS-022227, SMV, and ODV, will be determined by standard non-compartmental methods as appropriate. Population PK parameters (C_{0h} and AUC_{tau}) will be estimated by using non-linear mixed effects modeling. Separate SAPs will be made to describe the population PK methods.

The calculated values for all PK parameters will be tabulated by subject, by treatment and presented as graphs and by-subject listings. Computed PK parameters (primary and secondary) will be listed by subject and summarized by treatment group (mean, geometric mean, standard deviation, coefficient of variation, median, minimum, maximum, number of observations), as appropriate. PK parameters may be explored and the relationship between the measures of hepatic function (i.e., Child-Pugh score, albumin, bilirubin, and prothrombin time) and PK parameters may be assessed graphically. Additional analyses or summaries may be considered, as appropriate. Individual and mean (by time) concentrations versus time will be plotted by treatment group on both linear and natural logarithm scales.

Additional details for statistical consideration for PK analysis will be defined in the SAP.

10.6 Pharmacodynamic Analysis

Efficacy and safety parameters may be subjected to an exploratory PK/pharmacodynamic analysis as appropriate. AL-335, ALS-022399, ALS-022227, SMV, and ODV exposure versus efficacy and safety parameters may be subjected to an exploratory graphical analysis including various transformations in order to get a general overview, as appropriate.

Special attention will be paid to the plasma concentrations and PK parameters of those subjects who have discontinued the study for an AE, or who experienced a severe AE (at least Grade 3), or an SAE.

Additional details for statistical consideration for PK analysis will be defined in the SAP.

10.7 Efficacy Analysis

Efficacy will be determined by assessing HCV RNA results by time. Where appropriate, data will be pooled if identical regimens and patient populations are evaluated in multiple cohorts. Efficacy data will be summarized in tables and by subject listings, describing percent (un)detectable. Descriptive statistics will be utilized to summarize efficacy analyses.

Viral sequencing will also be analyzed to look for evidence of emergence of resistance. Pre-treatment polymorphisms in the HCV NS3/4A, NS5A and NS5B regions, as applicable, in all subjects and relevant changes in the HCV NS3/4A, NS5A and NS5B regions, as applicable, in subjects not achieving SVR will be tabulated and described. The effect of pre-treatment NS3/4A, NS5A and NS5B polymorphisms, as applicable, on treatment outcome will be explored. These changes in viral sequence will not be regarded as AEs or SAEs. Additional exploratory characterization of the viral sequence and phenotype may be performed and will be reported accordingly.

Please refer to the statistical analysis plan for more details.

10.8 Pooled Safety/Efficacy

To support initiation of a future Phase 3 study, safety, efficacy, and PK data from this study will be pooled with data from a separate Phase 2b (Omega-1) study. This will increase the sample size for the different duration groups and provide for more accurate estimates for safety and efficacy endpoints. The details of this combined analysis will be outlined in a separate analysis plan.

11.0 ADMINISTRATIVE CONSIDERATIONS

The investigator and/or Sponsor, consistent with local regulatory practice, will submit this protocol, the informed consent, Investigator's Brochure, and any other relevant supporting information to the competent authority and appropriate IRB/IEC for review and approval prior to study initiation. A letter confirming IRB/IEC approval of the protocol and informed consent, a statement that the IRB/IEC is organized and operates according to Good Clinical Practice (GCP) and the applicable laws and regulations, and financial disclosures (if applicable) **must** be forwarded to Alios BioPharma prior to screening subjects for the study. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, prior to the implementation of changes in this study.

11.1 Study Compliance

The study will be conducted in compliance with this protocol, principles of ICH GCP, Declaration of Helsinki, and all applicable national regulations governing clinical trials.

11.2 Informed Consent and Protected Subject Health Information Authorization

A copy of the IRB/IEC-approved informed consent must be forwarded to Alios BioPharma for regulatory purposes. The investigator or designee **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21CFR Part 50, European Union regulations (for European Union sites), and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated informed consent prior to enrollment into this study. Signed

consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance with individual local and national subject privacy regulations, the investigator or designee **must** explain to each subject prior to screening that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Alios BioPharma and its designees, regulatory agencies, and IECs/IRBs. As the study Sponsor, Alios BioPharma will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject prior to withdrawal will be used in the analysis of study results.

11.3 Subject Screening Log

The investigator **must** keep a record that lists **all** subjects considered for screening in the study. For those subjects subsequently excluded, record the reason(s) for exclusion.

11.4 Case Report Forms

Study site personnel will complete CRFs designed for this study according to the completion guidelines that will be provided. Paper CRFs should be completed in black or dark-blue ink. All corrections on paper CRFs will be made by drawing a single line through the information to be corrected, without obscuring it. All corrections will be initialed and dated (and explained, if necessary). Do not use "white-out" or obscuring correction fluid/tape to make changes. An electronic CRF (eCRF) may be used for this study. Study site personnel will be trained and authorized to use the system in compliance with 21 CFR Part 11 prior to recording data on eCRFs. All corrections to eCRFs will be made by authorized users, and the changes will be automatically logged in the system.

The investigator will ensure that the CRFs are accurate, complete, legible, and completed in a timely fashion. Separate source records are required to support all CRF entries. The CRF is not to be used to document data without prior written or electronic records. Case report forms should be completed for every subject enrolled in the study. At the study's conclusion, a PDF file will be created for each site containing their subjects' data submitted on eCRFs. In the event of an audit or regulatory authority inspection, copies of the eCRFs will be printed.

11.5 Study Monitoring Requirements

Representatives of Alios BioPharma or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff as well as any appropriate communications by mail, fax, e-mail, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to Quality Assurance reviews and/or audits under the Alios BioPharma Clinical Quality Assurance program.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of Alios BioPharma, its designated agent, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the ICF authorizing the use of protected health information.

11.6 Retention of Records

The investigator must retain a copy of all documents relating to this clinical trial for a minimum of 5 years after a marketing application is approved for the drug, unless Alios BioPharma notifies the investigator in writing that the documents no longer need to be retained because a marketing application will not be filed. The investigator must retain the documents for a longer period, where so required by other applicable requirements. Essential documents shall be archived in a way that ensures that they are readily available, upon request, to the competent authorities and appropriate regulatory authorities. The medical files of trial subjects shall be retained in accordance with national legislation and the maximum period of time permitted by the hospital, institution, or private practice. The investigator is responsible for contacting Alios BioPharma before any study-related documents are moved to another location or destroyed, and he or she must receive written approval from Alios BioPharma before such relocation or destruction of documents proceeds.

11.7 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 SMV, ACH3102 and AL-335, to understand chronic HCV GT1 infection, to understand differential drug responders, and to develop tests/assays related to SMV, ACH3102 and AL-335 and chronic HCV GT1 infection. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research.

11.8 Confidentiality and Publication Policy

By conducting this study, the investigator affirms to Alios BioPharma that all study results and information furnished by Alios BioPharma will be maintained in strict confidence. Such information will be communicated to the investigator's IRB/IEC under an appropriate understanding of confidentiality.

A published summary of the results of this study is, however, permissible according to Alios BioPharma and is not inconsistent with the preceding affirmation of confidentiality. Any publication of data collected as a result of this study will be considered a joint publication by the investigator and appropriate Alios BioPharma personnel. Authorship, including order, will be determined by Alios BioPharma in consultation with the Principal Investigator. Contribution of

the author to the study design, enrollment, data review, and manuscript preparation and review will be considered when determining the order of authorship for multicenter studies. Alios BioPharma must receive a copy of any presentation, manuscript, or abstract for review at least 45 days prior to public presentation or submission for publication. Any publication outside of this agreement is not permitted.

11.9 Conduct of Study and Protection of Human Subjects

The principal investigator must ensure the following (unless Sponsor is required per local regulations):

1. He or she will personally conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Staff Signature and Delegation of Authority log. The investigator will sign the authorization log whenever it is updated with new responsibilities or staff membership.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and permission to use protected health information are obtained from each subject prior to conducting study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/IEC and local competent authority comply with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the competent authority and IRB/IEC.
9. Any significant protocol deviations are reported to Alios BioPharma, the local competent authority and the IRB/IEC according to the guidelines at each study site.
10. All Safety Reports are submitted promptly to the local competent authority and IRB/IEC in accordance with the institution's internal policy.
11. All SAEs are reported within 24 hours of knowledge of the event, and to the local competent authority and the IRB/IEC.

12.0 REFERENCES

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13.0 APPENDICES

Appendix A. Investigator Signature Page

Study Acknowledgement

AL-335-604

A Phase 2a, Open-Label Study to Evaluate the Safety, Pharmacokinetics and Efficacy of the Combination of AL-335 and Odalasvir, with or without Simeprevir, in Treatment-Naïve Subjects with Genotype 1, 2 or 3 Chronic Hepatitis C infection with or without compensated Child Pugh A Cirrhosis

(VERSION 10.0, 03 May 2017)

This protocol has been approved by Alios BioPharma Inc. The following signature documents this approval.

John Fry,
VP Early Development

Name (Printed) [redacted] Signature

MAY 03, 2017

Date

Investigator Statement

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined in *Section 11.9 Conduct of Study and Protection of Human Subjects*, and will make every effort to complete the study within the time designated.

Principal Investigator Name (Printed) Signature

Date Site Name

Appendix B. Clinical Laboratory Evaluations

Chemistries: Albumin Bicarbonate BUN Calcium Chloride Cholesterol Creatinine Creatine Kinase Glucose Lipase LDH Phosphorus Potassium Sodium Total protein Triglycerides Uric acid Liver function tests: Alkaline phosphatase ALT AST Total bilirubin Direct bilirubin HbA1c Alpha fetoprotein Beta natriuretic peptide (BNP) or NT-pro-BNP	**Hematology (CBC):** Hematocrit Hemoglobin MCH MCHC MCV MPV Platelet count RDW Red blood cell count Reticulocytes White blood cell count White blood cell differentiation (percentage and ABS) Basophils Eosinophils Lymphocytes Monocytes Neutrophils
Coagulation: PT/INR PTT	
Urinalysis (UA): Color and appearance — Nitrite pH and SG — Occult blood/hematuria Bilirubin — Protein Glucose — Urobilinogen Ketones Leukocytes Microscopic (inc RBSs and WBCs)- reflex test only	**In-house Drug Screen:** Methadone Amphetamines Barbiturates Cocaine Opiates Phencyclidine Benzodiazepines
Females only: Pregnancy Test FSH and estradiol to be collected at Screening only	**Other Tests:** HAV IgM HBsAg HBsAb HBcAb HCVAb HIVAb HCV RNA

Appendix C. Blood Volumes for Week 4 Cohort

Interval / Assessments	Day				Week				Follow-up Week				
	Screen -50 to -1	**1**	**2**	**3**	**1**	**2**	**3**	**4**	**4 (±1 wk)**	**8 (±1 wk)**	**12 (±2 wk)**	**18 (±2 wk)**	**24 (±2 wk) Completion**
Drug Screen	2												
Hepatitis and HIV screen (HBsAg, HBsAB, HBcAb, HCVAb, HIVAb)	10												
HCV genotype	3												
IL28B determination		3											
PK Samples		6				60	12	12	2	2	2	2	2
Liver Function Tests	2	2			2	2	2	2	2				
CBC w/diff PT/PTT & INR and Urinalysis, Serum Chemistry	25	25			25	25		25	25				
HCV RNA concentration	6	6	6	6	6	6	6	6	6	6	6	6	6
Plasma for drug resistance monitoring		8	8	8	8	8	8	8	8	8	8	8	8
Pregnancy Test	2	2						2	2	2	2		2
Alpha-fetoprotein, glycosylated HbA1C	7												
Stored serum sample	4	4			4	4	4	4	4				
Totals	**61**	**56**	**14**	**14**	**45**	**105**	**32**	**59**	**49**	**18**	**18**	**16**	**18**

Ab=antibody; CBC=complete blood count; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IL28B=interleukin 28B ; INR=International Normalization Ratio; PK=pharmacokinetic; PT=prothrombin time; PTT=partial thromboplastin time.

Note: Estimated total volume is ~ 505 mL. Note that volumes are approximate. There may be some variation in the volumes that are required between laboratories at different clinical trial centers

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Appendix D. Blood Volumes for Week 6 Cohort

Interval / Assessments	Day				Week						Follow-up Week				
	Screen -50 to -1	1	2	3	1	2	3	4	5	6	4 (±1 wk)	8 (±1 wk)	12 (±2 wk)	18 (±2 wk)	24 (±2wk) Completion
Drug Screen	2														
Hepatitis and HIV screen (HBsAg, HBsAB, HBcAb, HCVAb, HIVAb)	10														
HCV genotype	3														
IL28B determination		3													
PK Samples		6				60	12	12		12	2	2	2	2	2
Liver Function Tests	2	2			2	2	2	2	2	2	2				
CBC w/diff PT/PTT & INR and Urinalysis, Serum Chemistry	25	25			25	25		25		25	25				
HCV RNA concentration	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Plasma for drug resistance monitoring		8	8	8	8	8	8	8	8	8	8	8	8	8	8
Pregnancy Test	2	2						2			2	2	2		2
Alpha-fetoprotein, glycosylated HbA1C	7														
Stored serum sample	4	4			4	4	4	4	4	4	4				
Totals	**61**	**56**	**14**	**14**	**45**	**105**	**32**	**59**	**20**	**57**	**49**	**18**	**18**	**16**	**18**

Ab=antibody; CBC=complete blood count; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IL28B=interleukin 28B ; INR=International Normalization Ratio; PK=pharmacokinetic; PT=prothrombin time; PTT=partial thromboplastin time.

Note: Estimated total volume is ~582 mL. Note that volumes are approximate. There may be some variation in the volumes that are required between laboratories at different clinical trial centers.

Appendix E. Blood Volumes for Week 8 or 12* Cohort

Interval / Assessments	Day				Week								Follow-up Week				
	-50 to -1 Screen	1	2	3	1	2	3	4	5	6	7	8	4 (±1 wk)	8 (±1 wk)	12 (±2 wk)	18 (±2 wk)	24 (±2 wk) Completion
Drug Screen	2																
Hepatitis and HIV screen (HBsAg, HBsAB, HBcAb, HCVAb, HIVAb)	10																
HCV genotype	3																
IL28B determination		3															
PK Samples		6				60	12	12		12		12	2	2	2	2	2
Liver Function Tests	2	2			2	2	2	2	2	2	2	2	2				
CBC w/diff PT/PTT & INR and Urinalysis, Serum Chemistry	25	25			25	25		25		25		25	25				
HCV RNA concentration	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Plasma for drug resistance monitoring		8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Pregnancy Test	2	2						2				2	2	2	2		2
Alpha-fetoprotein, glycosylated HbA1C	7																
Stored serum sample	4	4			4	4	4	4	4	4	4	4	4				
Totals	**61**	**56**	**14**	**14**	**45**	**105**	**32**	**59**	**20**	**57**	**20**	**59**	**49**	**18**	**18**	**16**	**18**

Ab=antibody; CBC=complete blood count; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IL28B=interleukin 28B ; INR=International Normalization Ratio; PK=pharmacokinetic; PT=prothrombin time; PTT=partial thromboplastin time.

Note: Week 8 estimated total volume is ~661 mL. Note that volumes are approximate. There may be some variation in the volumes that are required between laboratories at different clinical trial centers.

* If a 12-week regimen is evaluated, the Week 5, 6, 7, and 8 visits will be repeated at Weeks 9, 10, 11, and 12, respectively. Week 12 estimated total volume is ~817 mL. Note that volumes are approximate. There may be some variation in the volumes that are required between laboratories at different clinical trial centers

Appendix F. Toxicity Tables

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS. PUBLISH DATE: NOVEMBER, 2014

Introduction

The Division of AIDS (DAIDS) oversees clinical trials throughout the world which it sponsors and supports. The clinical trials evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

The DAIDS AE grading table is a shared tool for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in clinical trials. Over the years as scientific knowledge and experience have expanded, revisions to the DAIDS AE grading table have become necessary.

The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0* replaces the grading table published in 2004 and updated in 2009. In version 2.0, AEs not previously included, but which now are deemed medically important events, are included while other AEs have been removed. Some AE severity grading descriptions have been revised to more appropriately reflect the presentation of these events in clinical settings and their impact on clinical trials. For example, DAIDS performed an extensive literature search and reviews of select DAIDS clinical trial data in revising certain hematology parameters (i.e., hemoglobin, white cell counts, and absolute neutrophil counts). DAIDS also took into consideration the U.S. Food and Drug Administration's guidance regarding the use of local laboratory reference values and ethnic differences among certain healthy adolescent and adult populations in defining parameter limits. Finally, the revised DAIDS AE grading table also contains an updated glossary and acronyms section, an expanded instructions for use section, and an appendix that provides more age-specific information for an AE of concern to DAIDS.

DAIDS is grateful to the DAIDS Grading Table Working Group, numerous government and non-government affiliated medical subject matter experts and reviewers who were instrumental in the revision of the DAIDS AE grading table.

Glossary and Acronyms

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young Children Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

Glossary and Acronyms

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. Young Children Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Instructions for Use

General Considerations

The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS AE grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

The DAIDS AE grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death (*Note*: This grade is not specifically listed on each page of the grading table).

Other points to consider include:

- Use parameters defined by age and sex values as applicable.
- Male and female sex are defined as sex at birth.
- Unless noted, laboratory values are for term neonates. Preterm neonates should be assessed using local laboratory normal ranges.
- Where applicable, Standard International (SI) units are included in italics.

Selecting and Reporting a Primary AE Term

When selecting a primary AE term to report, sites should select the term that best describes what occurred to the participant. For example, a participant may present with itching, urticaria, flushing, angioedema of the face, and dyspnea. If the underlying diagnosis is determined to be an acute allergic reaction, sites should report "Acute Allergic Reaction" as the primary AE term.

Primary AE terms should be reported using the DAIDS Adverse Experience Reporting System (DAERS) only if they meet expedited reporting criteria. However, all primary AE terms should be reported using protocol-specific case report forms (CRFs). Because the reported information is stored in different databases (i.e., safety and clinical), sites should report primary AE terms using the same terminology for data consistency.

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When reporting using DAERS, other clinically significant events associated with a primary AE term that more fully describe the nature, severity, or complications of the primary AE term should be entered in the "Other Events" section. However, the severity grade for these events must be lower than or equal to the severity grade of the primary AE term. In the example above, dyspnea and angioedema of the face may be entered in the "Other Events" section, because they are more descriptive and provide additional information on the severity of the acute allergic reaction. However, their severity grades must be lower than or equal to the severity grade of the primary AE term of "Acute Allergic Reaction".

Differences exist in the reporting and recording of information (e.g., signs and symptoms, clinically significant events) in DAERS and CRFs. Therefore, sites should refer to their protocols and CRF requirements for further instructions.

Grading Adult and Pediatric AEs
When a single parameter is not appropriate for grading an AE in both adult and pediatric populations, separate parameters with specified age ranges are provided. If no distinction between adult and pediatric populations has been made, the listed parameter should be used for grading an AE in both populations.

Reporting Pregnancy Outcomes
In the *Pregnancy, Puerperium, and Perinatal* section, all parameters are pregnancy outcomes and should be reported using the mother's participant ID. If an infant is not enrolled in the same study as the mother, any identified birth defects should be reported using the mother's participant ID. However, if an infant is enrolled in the same study as the mother or in another study, any identified birth defects should be reported using the infant's participant ID. Sites should refer to the applicable network standards for reporting abnormal pregnancy outcomes on the CRFs.

Determining Severity Grade for Parameters between Grades
If the severity of an AE could fall in either one of two grades (i.e., the severity of an AE could be either grade 2 or grade 3), sites should select the higher of the two grades.

Laboratory Values
General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the CRFs.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory

Instructions for Use

value. For example, "Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory's normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant's magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Appendix Usage
Appendix A takes priority over the main grading table in all assessments of total bilirubin for term and preterm neonates.

Using Addenda 1-3: Grading Tables Used in Microbicide Studies
In protocols involving topical application of products to the female and male genital tracts or rectum, strong consideration should be given to using Addenda 1-3 (see below) as the primary grading tables for these areas. Although these grading tables are used specifically in microbicide studies, they may be used in other protocols as adjuncts to the main grading table (i.e., the *Division of AIDS (AIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0*). It should be clearly stated in a protocol which addendum is being used as the primary grading table (and thus takes precedence over the main grading table) and which addendum is being used in a complementary fashion.

- Addendum 1 – Female Genital Grading Table for Use in Microbicide Studies – PDF
- Addendum 2 – Male Genital Grading Table for Use in Microbicide Studies – PDF
- Addendum 3 – Rectal Grading Table for Use in Microbicide Studies – PDF

Estimating AE severity grade for events not identified in the Grading Table or Laboratory Abnormalities which are considered AEs

AEs not defined by the DAIDs toxicity table and laboratory abnormalities which are considered AEs, should be graded according to the following scale, which considers key clinical parameters (e.g. symptoms, functional status, need for intervention) and is also defined by the DAIDs scale:

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

NOTE: Laboratory abnormalities may have their grading defined in the DAIDS table below, however, all laboratory abnormalities do not necessarily represent an adverse event. If a laboratory abnormality is considered an AE, the AE need not have the same grade as the laboratory abnormality itself. The AE grade for a laboratory abnormality should be defined by the table above.

Major Clinical Conditions
Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1] *Hypertension (with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A delivery of a live-born neonate occurring at ≥ 20 to < 37 weeks gestational age.
[8] Definition: A clinically recognized pregnancy occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medicamylasal intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[9]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[10] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[11]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)

[9] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[10] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).
[11] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Underweight[12] *> 5 to 19 years of age*	NA	WHO BMI z-score < -2 to ≤ -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	NA	WHO Weight-for-height z-score < -2 to ≤ -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	NA	WHO Weight-for-length z-score < -2 to ≤ -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[12] WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those < 5 years of age.

Site Reactions to Injections and Infusions

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

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Laboratory Values
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	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
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[14], High*** *> 28 days of age*	NA	NA	> ULN	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*

[14] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10 x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Creatinine Clearance[15] **or eGFR, Low** *Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR ≥ 30 to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Glucose, Low (mg/dL; *mmol/L*) *≥ 1 month of age*	55 to 64 *3.05 to 3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences

[15] Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipase, High	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
Lipid Disorders (mg/dL; *mmol/L*)				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High				
≥ 18 years of age	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[16], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.81 to < LLN*	1.4 to < 2.0 *0.65 to < 0.81*	1.0 to < 1.4 *0.32 to < 0.65*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 135*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

[16] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*)				
> 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*)				
> 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[17], Low (g/dL; *mmol/L*)[18]				
≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

[17] Male and female sex are defined as sex at birth.
[18] The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Appendix A.
Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[19], High (mg/dL; *µmol/L*)[20]				
Term Neonate[21] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[19] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.
[20] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.
[21] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

Appendix G. Child-Pugh Score

The score employs 5 clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

Measure	1 Point	2 Points	3 Points
Total bilirubin, µmol/L (mg/dL)	<34 (≤2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.

Points	Class
5-6	A
7-9	B
10-15	C

Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60 (8):646–9.