Title:	**Open-label Rollover Study of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects with Nonalcoholic Steatohepatitis (NASH)**
Protocol Number:	**3152-201-002**
Product:	**Cenicriviroc (CVC)**
Phase of Study:	**2**
Sponsor:	**Tobira Therapeutics, Inc., a subsidiary of Allergan plc 701 Gateway Blvd, Suite 300 South San Francisco, CA 94080 United States of America**
EudraCT Number:	**2016-004754-15**
Date of Protocol	**01 December 2016**
Date of Global Amendment 1	**14 Apr 2018**

Purpose of Amendment

The purpose of Global Protocol Amendment 1 (dated 14 Apr 2018) for Study 3152-201-002 is to provide details regarding the rollover of additional subjects from the AURORA Study (3152-301-002) into Study 3152-201-002.

A summary of changes is provided in Table 1-1. Additional administrative edits were also made, but not specifically noted (eg, corrected spelling, punctuation, grammar, abbreviation, and style errors) including global edits required for consistency (eg, "study drug", "subjects", abbreviation use).

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of subjects nor the scientific value of the study.

Table 1-1 Summary of Changes in Global Protocol Amendment 1

Protocol Sections	Summary of Changes	Rationale for Changes
Section 1 Emergency Contacts	Added "Adverse Events of Special Interest"	Administrative addition for completeness.
Section 4 Synopsis; Section 5.4 Study Rationale; Section 7.1 Overall Study Design and Plan;	Added text to clarify eligibility criteria for subjects from AURORA (3152-301-002) entering this study (3152-201-002). Subjects from the following studies will be eligible to receive open-label CVC 150 mg once daily: • Subjects who have completed both Treatment Period 1 and Treatment Period 2 (Year 1 and Year 2), of the CENTAUR study (652-2-203), regardless of their treatment assignment in the CENTAUR study (CVC or placebo). • Subjects who have completed the AURORA study (3152-301-002) as a result of progression to cirrhosis or reaching an adjudicated liver-related clinical outcome in either Part 1 or Part 2 of the study, regardless of their treatment assignment (CVC or placebo). Refer to Section 8.2 for additional details.	Revision needed to enable subjects from AURORA to enter the study.

Protocol Sections	Summary of Changes	Rationale for Changes
	Section 5.4: The open-label rollover protocol will be conducted to offer continued access to CVC to subjects who completed the CENTAUR study, progressed to cirrhosis, or reached an adjudicated liver related clinical outcome and completed the AURORA study.	
Section 4 Synopsis; Section 7.1 Overall Study Design and Plan	Removed the specific regions involved from the synopsis; updated approximate number of study centers.	Administrative revision.
Section 4 Synopsis; Section 8.1 Number of Subjects	Number of subjects was updated to include those from both CENTAUR and AURORA.	Subjects from both CENTAUR and AURORA sites are included in this study.
Section 4 Synopsis;	Updated target population to include those from both CENTAUR and AURORA.	Subjects from both CENTAUR and AURORA sites are included in this study.
Section 4 Synopsis; Section 8.2 Inclusion Criteria (#1, 2,)	Revised text to clarify eligibility criteria for subjects from AURORA (3152-301-002) and CENTAUR (652-2-203) to enter this study (3152-201-002). IC 1: Subjects who have either: • Completed both Treatment Period 1 and Treatment Period 2 (Year 1 and Year 2) of the CENTAUR study (652-2-203), including a Year 2 liver biopsy • Completed the AURORA study (3152-301-002) as a result of reaching an adjudicated liver-related clinical outcome in Part 1 or Part 2 of the study of: o Histopathologic progression to cirrhosis o MELD score ≥ 15 o Ascites (requiring intervention, ie, large volume paracentesis ≥ 1L or initiation of a diuretic) o Hospitalization (as defined by a stay of ≥ 24 hours) for onset of: variceal bleed, hepatic encephalopathy (defined by a West Haven Stage of ≥ 2), spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis with positive ascitic fluid bacterial culture)	Revision needed to enable subjects from AURORA to enter the study #1: Revised text to clarify eligibility criteria for subjects from AURORA to enter this study.

Protocol Sections	Summary of Changes	Rationale for Changes
	IC 2: Has been determined to be in a stable medical condition (minimum of approximately 3 months from the date of the clinical event in AURORA to the Baseline Visit of this study) based on medical history or physical examination, in the opinion of investigator. Inclusion criterion applies only to subjects coming from the AURORA study (3152-301-002).	#2: To ensure qualified participants rollover into this study.
[redacted]		

Protocol Sections	Summary of Changes	Rationale for Changes
[redacted]		
Section 4 Synopsis; Section 10.1 Baseline	Added text to clarify eligibility criteria for subjects from AURORA (3152-301-002) entering this study (3152-201-002). Subjects will be required to rollover to this continued access study within 1 month of completing their final visit assessments in either the CENTAUR study or the AURORA study. Eligible subjects who completed these studies, prior to initiation of this protocol at their study center, will be allowed to participate in this rollover study.	Text edited to align with revisions needed to enable subjects from AURORA to enter the study
Section 4 Synopsis; Section 12 Statistics	Text updated to reflect there would be no inferential statistical testing.	Administrative revision for accuracy.
Section 4 Synopsis	Sample size was updated to reflect approximate number of subjects.	Subjects from both CENTAUR and AURORA sites are included in this study
Section 5.3 Clinical Studies with CVC	Updated text to reflect updated numbers of patients exposed to CVC per January 2018 Development Safety Update Report [DSUR] cutoff	Provides updated exposure numbers and aligns with AURORA.

Protocol Sections	Summary of Changes	Rationale for Changes
Section 5.3.1 Phase 1 Pharmacokinetic Studies in Healthy Subjects	Section was rewritten to align with AURORA.	Section was revised to align with AURORA.
Section 5.3.3 Phase 2b Study in Subjects with NASH and Liver Fibrosis	Section was rewritten to align with AURORA.	Revisions required to capture up-to-date information for this rollover study, to distinguish information specific to Treatment Period 2 (Year 2) and Treatment Period 1 (Year 1), and to align with AURORA.
Section 7.1; Overall Study Design and Plan (Figure 7-1)	Deleted CENTAUR specific text and updated footnotes.	Revisions to Figure 7-1 Study Design Schematic required to accurately reflect rollover study.
Section 9.1 Treatments Administered; Section 9.2.4 Study Drug Dispensing and Collection; Section 9.4 Study Drug with food Administration; Section 11.2 Assessments of Drug Accountability and Medication Adherence	Deleted text instructing subjects to take the study drug in the morning and clarified they are to take 1 table.	Revised for accuracy.
Section 9.2.2 Packaging and Labeling; Section 9.8 Treatment Adherence; Appendix 20.1 Schedule of Assessments	Added text specifying visit window (± 2 weeks)	Administrative revision.
[redacted]		
Section 9.2.5 Investigational Product Accountability	Deleted text regarding destruction of study drug and referred readers to the Pharmacy Manual.	Administrative revision
Section 9.3 Randomization	Clarified subjects will retain their subject identification number from either the CENTAUR study or AURORA study.	Edited to reflect retention of subject identification numbers.
Section 9.6 Prior and Concomitant Therapy; Appendix 20.4 Disallowed Medications	Revisions to text were made to align with AURORA.	Updated to mirror content and revisions in the more recent AURORA protocol.
Section 9.7 Additional Restrictions and Precautions; Section 10.1 Baseline	Deleted text regarding photosensitivity.	Text regarding photosensitivity was removed for consistency with AURORA.
Section 10.3 Discontinuation Visit	Deleted “Early” when referring to Discontinuation Visit.	Revisions needed to align with changes to the Schedule of Assessments
Section 10.3 1-Month Follow-up and Section 10.4 Discontinuation Visit	Reversed the order of sections so Discontinuation Visit precedes 1-Month Follow-up	Revisions needed to align with changes to the Schedule of Assessments.

Protocol Sections	Summary of Changes	Rationale for Changes
Section 10.6 Criteria for Discontinuation of Study Treatment	Edited text to read as follows: Study drug must be discontinued in the following instances: • Confirmation of ALT or AST elevations meeting the following criteria for suspected DILI[23] (the required confirmatory measurement should be obtained within 48 to 72 hours after the laboratory results become available): o When the baseline values are < 2 × ULN, discontinue if ALT and/or AST increases to >3 × ULN and > 5 × baseline measure o When the baseline values are ≥ 2 × ULN but < 5 x ULN, discontinue if ALT and/or AST increases to > 3 × baseline measure ~~o~~ When the baseline values are ≥ 5 × ULN, discontinue if ALT and/or AST increases to > 2 × baseline measure	Section was revised to align with AURORA.
Section 11.1.1.1.2 Treatment-Emergent Adverse Events; Section 12.1 Safety	Added definition of TEAE Clarified data involving TEAEs	Included for completeness and clarification.
Section 11.1.1.1.9 Overdose	Edited text to read as follows: An overdose is defined as a subject's report of taking more than 1 tablet of study drug (ie, more than 1 tablet per day of CVC). Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. For reporting purposes, overdose will be considered an SAE only if any of the seriousness criteria are met (see definition in Section 11.1.1.1.10).	Included for completeness and clarification.
Section 11.1.1.1.11 Adverse Events of Special Interest	Added text defining AEs of Special Interest and reporting requirements.	Included to align more closely with CPT and other NASH protocols.
Section 11.1.1.5 Reporting of Serious Adverse Events	Deleted specific directions where to send completed Safety Report Forms and referred Section 1 for contact information.	

Protocol Sections	Summary of Changes	Rationale for Changes
Section 11.1.1.6 Follow-up of AEs and SAEs	Added text expanding the definition of which subjects should have a PK sample obtained.	Included for completeness and clarification.
Section 11.1.2.1 Measurement of Laboratory Assessments	Clarified site performing urine pregnancy testing.	Administrative revision
Section 11.1.3.2 Grade 3 Laboratory Abnormality or Clinical Event; Excluding ALT and AST; Section 11.1.3.3 Grade 4 Laboratory Abnormality or Clinical Event; Excluding ALT and AST	ALP and bilirubin were added. Text was edited to include "Confirmatory measurements to be obtained within 48 to 72 hours of re-occurring Grade 3 laboratory abnormalities considered clinically nonsignificant, unrelated to study drug, and associated with pre-existing medical history should be performed per the discretion of the investigator and in consultation with the medical monitor."	Edits made for clarification and alignment with AURORA.
[redacted]		
Appendix 20.1 Schedule of Assessments	Deleted "Period and Open-label Treatment" as table headers. Added Discontinuation Visit and corresponding footnote. Clarified footnote regarding rollover requirements. Added footnotes clarifying continuation of study visits, and defining subject visit window. Included obtaining FSH from postmenopausal women only. Deleted the Note in footnotes; deleted "early" when describing the Discontinuation Visit. Renumbered footnotes as needed.	Not applicable Needed as part of study design. Needed to align with descriptive within the Schedule of Assessment table.
[redacted]		

Protocol Sections	Summary of Changes	Rationale for Changes
Appendix 20.4 Disallowed Medications	Revised the list and tables of disallowed medications. Added a table identifying drugs to be taken with precaution during intake of study drug. Revision now allow for coadministration of P-gp inhibitors with CVC.	Modifications required for consistency with AURORA
[redacted]		

1. EMERGENCY CONTACTS

In emergency situations, the investigator should contact the clinical research associate or medical monitor assigned to the site. Please refer to the site study binder for contact details.

Serious Adverse Event/Pregnancy Reporting/Adverse Events of Special Interest

Email: [redacted]
Fax: [redacted]
(Back-up Fax: [redacted]

2. TABLE OF CONTENTS

2.1. List of In-Text Tables

2.2. List of In-Text Figures

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event(s) of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BUN	blood urea nitrogen
CCR	C-C chemokine receptor
CI	confidence interval
C_{max}	maximum concentration of drug
C_{min}	minimum plasma concentration
CPK	creatine phosphokinase
CRN	Clinical Research Network
CVC	cenicriviroc
CYP	cytochrome P450
DILI	drug-induced liver injury
$EC_{min}50$	half-maximal response
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HCC	hepatocellular carcinoma
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
INR	international normalized ratio
IRB	Institutional Review Board

Abbreviation	Definition
ITT	intent-to-treat
LC1	liver cytosol type 1
LDH	lactate dehydrogenase
LKM1	liver/kidney microsome type 1
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
MIP	macrophage inflammatory protein
mITT	modified intent-to-treat
NAFLD	nonalcoholic fatty liver disease
NAS	a nonalcoholic fatty liver disease activity score
NASH	nonalcoholic steatohepatitis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	pharmacodynamic
P-gp	P-glycoprotein
PK	pharmacokinetic
PPI	proton pump inhibitor
RANTES	regulated on activation normal T-cell expressed and secreted
SAE	serious adverse event
SAR	suspected adverse reaction
SMA	smooth muscle antibodies
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
T2DM	type-2 diabetes mellitus
TE	transient elastography
TEAE	treatment-emergent adverse event
t_{max}	time to maximum plasma concentration
Tobira	Tobira Therapeutics, Inc., a subsidiary of Allergan plc
ULN	upper limit of normal
US	United States

4. SYNOPSIS

Title	Open-label Rollover Study of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects with Nonalcoholic Steatohepatitis (NASH)
Study Number	3152-201-002
Clinical Phase	2
Indication	Treatment of liver fibrosis in adult subjects with NASH
Objectives	Study Objectives: • To provide open-label treatment with cenicriviroc (CVC) to subjects who have previously participated in CVC studies • To assess the long-term safety of continued treatment with CVC for subjects who have previously participated in CVC studies
Study Design	Subjects from the following studies will be eligible to receive open-label CVC 150 mg once daily: • Subjects who have completed both Treatment Period 1 and Treatment Period 2 (Year 1 and Year 2) of the CENTAUR study (652-2-203), regardless of their treatment assignment in the CENTAUR study (CVC or placebo). • Subjects who have completed the AURORA study (3152-301-002) as a result of progression to cirrhosis or reaching an adjudicated liver-related clinical outcome in either Part 1 or Part 2 of the study regardless of their treatment assignment (CVC or placebo). Refer to Section 8.2 for additional details. Subjects will be required to rollover to this continued access study within 1 month of-completing their final visit assessments in either the CENTAUR or AURORA study. Eligible subjects who completed these studies, prior to initiation of this protocol at their study center, will be allowed to participate in this rollover study. Subjects will attend regular study visits for continued safety assessment at the start of this open-label rollover study (Baseline), then every 3 months thereafter for the duration of the study, or at the discretion of the investigator. A central laboratory will be used for laboratory assessments.
Treatment Duration	This is a rollover study in which CVC treatment will continue to be provided until it is commercially available or if development is terminated, as applicable.
Number of Subjects	It is expected that a total of approximately 560 subjects may rollover from both the CENTAUR study (652-2-203) and the AURORA study (3152-301-002).
Number of Study Centers	Up to approximately 480 centers
Target Population	Adult subjects with NASH who have completed both Treatment Period 1 and Treatment Period 2 in the CENTAUR study (652-2-203), or who have completed the AURORA study (3152-301-002) as a result of progression to cirrhosis or reaching an adjudicated liver-related clinical outcome in either Part 1 or Part 2 of the study.

Inclusion Criteria	1. Subjects who have either: • Completed both Treatment Period 1 and Treatment Period 2 (Year 1 and Year 2) of the CENTAUR study (652-2-203), including a Year 2 liver biopsy. • Completed the AURORA study (3152-301-002) as a result of reaching an adjudicated liver-related clinical outcome in Part 1 or Part 2 of the study of: o Histopathologic progression to cirrhosis o Model for end-stage liver disease (MELD) score ≥ 15 o Ascites (requiring intervention, ie, large volume paracentesis ≥ 1L or initiation of a diuretic) o Hospitalization (as defined by a stay of ≥ 24 hours) for onset of: variceal bleed, hepatic encephalopathy (defined by a West Haven Stage of ≥ 2), spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis with positive ascitic fluid bacterial culture) 2. Has been determined to be in a stable medical condition (minimum of 3 months from the date of the clinical event in AURORA to the Baseline Visit of this study) based on medical history or physical examination, in the opinion of investigator. Inclusion criterion applies only to subjects coming from the AURORA study (3152-301-002). [redacted]
Exclusion Criteria	[redacted] 2. Prior or planned liver transplantation 3. Other known causes of chronic liver disease, such as the following: • Alcoholic liver disease • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune hepatitis • Wilson's disease, hemochromatosis, or iron overload • Alpha-1-antitrypsin (A1AT) deficiency [redacted]

	
Test Article	CVC 150-mg tablet
Dosage and Administration	Open-label CVC 150 mg, administered orally once daily with food.
Reference Therapy	Not applicable
Study Procedures/ Frequency	• Scheduled laboratory tests (serum chemistries and hematologic assessments) will be performed at Baseline and every 3 months (Months 3, 6, 9, 12, 15, 18, 21, 24 etc., until CVC becomes commercially available or if development is terminated). A central laboratory will be used to process blood/serum samples. • Subject safety will be assessed at scheduled study visits. Unscheduled visits may also be used, at the discretion of the investigator.
Safety Evaluation	A central laboratory will be used for laboratory assessments which are required per protocol. All adverse events (AEs), adverse drug reactions (ADRs) serious adverse events (SAEs), suspected unexpected serious adverse reactions (SUSARs), and treatment discontinuation due to AEs will be collected. Long-term safety with CVC will be assessed.
Statistical Analysis	No inferential statistical testing will be conducted for this continued access study. Summaries of demographics, baseline characteristics, treatment exposure and safety parameters will be analyzed by descriptive statistics for the continuous variables and frequency counts with incidence rates for the dichotomous or categorical variables.
Sample Size	Approximately 560 subjects are expected to roll over from both the CENTAUR study (652-2-203) and the AURORA study (3152-301-002) to receive open-label CVC.

5. INTRODUCTION

Cenicriviroc mesylate (CVC) is a novel, once-daily, orally active and potent inhibitor of ligand binding to C-C chemokine receptor (CCR) type 2 (CCR2) and type 5 (CCR5), currently in clinical development for the treatment of liver fibrosis in adult subjects with nonalcoholic steatohepatitis (NASH).

5.1. Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Nonalcoholic fatty liver disease (NAFLD) is a common, often "silent," liver disease associated with obesity-related disorders, such as type-2 diabetes mellitus (T2DM) and the metabolic syndrome, occurring in people who consume little or no alcohol, and is characterized by the accumulation of fat in the liver with no other apparent causes.[1-11] At the beginning of the NAFLD spectrum is simple or bland steatosis, which is characterized by a build-up of fat within the liver. Liver steatosis without inflammation is usually described as benign or nonprogressive. NASH is usually described as a severe form of NAFLD where steatosis is complicated by liver-cell injury and inflammation, with or without fibrosis. The rising prevalence of obesity-related disorders has contributed to a rapid increase in the prevalence of NASH. Approximately 10% to 20% of subjects with NAFLD will progress to NASH.[12] Due to the growing epidemic of obesity and diabetes worldwide, NASH is projected to become the most common cause of advanced liver disease and the most common indication for liver transplantation.[13-16] The burden of NASH, combined with a lack of any approved therapeutic interventions, represents an unmet medical need.

5.2. CVC Mechanism of Action

In vitro data with CVC has demonstrated that it blocks the binding of C-C motif chemokine ligand 2 (CCL2; also known as monocyte chemotactic protein 1 [MCP-1]) to CCR2, and also blocks the binding of CCR5 ligands, CCL3 (also known as macrophage inflammatory protein [MIP]-1α), CCL4 (also known as MIP-1β) and CCL5 (also known as regulated on activation normal T-cell expressed and secreted [RANTES]), to CCR5. Ex vivo experiments showed that nanomolar concentrations of CVC achieved 98% receptor occupancy of CCR2 on human monocytes and ~90% receptor occupancy for CCR5 on human CD4+ and CD8+ T-cells. Additionally, CVC was an efficient inhibitor of monocyte and human lymphocyte (primarily T-cells) migration in vitro.

The mechanistic rationale for the use of CVC as an anti-inflammatory and anti-fibrotic agent in liver disease, such as liver fibrosis associated with NASH, is as follows. First, CVC treatment decreases the recruitment and migration of CCR2-expressing monocytes to the site of liver injury, mainly via CCR2 antagonism, thereby reducing the infiltration of pro-inflammatory, monocyte-derived macrophages into the liver.[17,18] Second, CCR5 antagonism by CVC is expected to impair the migration, activation, and proliferation of collagen−producing activated hepatic stellate cells and myofibroblasts, therefore reducing fibrogenesis.[19,20]

5.3. Clinical Studies with CVC

Overall, as of January 2018, approximately 1154 subjects have been exposed to CVC in completed and ongoing clinical studies (January 2018 Development Safety Update Report [DSUR] cutoff).

5.3.1. *Phase 1 Pharmacokinetic Studies in Healthy Subjects*

Initial human pharmacokinetic (PK) data for CVC was obtained in 2003 when the molecule was being developed by Takeda Pharmaceutical. The first 2 Phase 1 studies of CVC (Study 2080/16 [RCP-001] and Study 001 [01-03-TL-652-001]) established CVC's bioavailability in humans and demonstrated that CVC was not excreted in urine, that plasma drug exposure was nearly dose proportional up to single doses of 400 mg, and that M-II and M-I were the major and minor metabolites, respectively, in humans. More importantly, the studies established rapid attainment of clinically significant drug levels, with a time to maximum plasma concentration (t_{max}) of 3 to 6 hours, and the possibility of once-daily dosing with a half-life ($t_{1/2}$) of 34 to 42 hours.

Tobira conducted its first clinical study with CVC tablet formulation at doses up to 800 mg in 2008 (Study 652-1-101) and confirmed that CVC was readily absorbed with median t_{max} occurring about 3 to 6 hours postdose across the dose levels. CVC was eliminated from plasma with a mean $t_{1/2}$ of approximately 30 to 40 hours across the wide dose range studied, suggesting linear elimination kinetics. Evaluation of single oral dose administration of the Phase 3 formulation of CVC 150 mg in Study 3152-101-002 suggested that food increases exposure of CVC by 5.2-fold with a mean $t_{1/2}$ of approximately 40 hours.

CVC was well tolerated in all of the single-dose studies, with no clinically important findings with respect to vital signs, electrocardiogram (ECG) findings, physical examinations, or laboratory tests for any subject. A few subjects had mild, usually isolated elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) while on CVC.

Study 102 (652-1-102) was the first multiple-dose study in humans. This randomized, double-blind, placebo-controlled, multiple-dose study was conducted in cohorts of 12 healthy adult male and female subjects. In Part 2 of Study 102, CVC at doses of 25 to 200 mg once daily was readily and well absorbed following single (Day 1) or repeated (Day 10) doses with a high-fat meal, achieving peak plasma concentrations about 3 to 6 hours postdose. The mean $t_{1/2}$ of CVC following repeated doses was similar to that after a single dose, averaging approximately 35 to 40 hours across dose regimens, indicating that the elimination kinetics of CVC were unchanged following repeated doses.

In Study 102, 2 subjects experienced adverse events (AEs) that resulted in discontinuation of study drug: Grade 4 AST/ALT in 1 subject, and a Grade 2 AST elevation and an elevated lactate dehydrogenase (LDH) in the other subject.

The safety, tolerability, and PK of the Phase 3 formulation following once daily escalating doses of CVC (450 and 900 mg) and combination with a single dose of 100 mg ritonavir were evaluated in Study 3152-107-002. Steady state levels of CVC, M-1, and M-II metabolites were achieved with once daily dosing of 450 or 900 mg CVC with a high-fat

meal for 7 days. Comparison of PK parameters suggested dose-proportional increase in maximum concentration of drug (C_{max}) and $AUC_{0-\tau}$ of CVC and M-1 metabolite, while M-II exposure increased less than proportionally. Coadministration of CVC with a single dose of 100 mg ritonavir resulted in increased CVC C_{max} and $AUC_{0-\tau}$ by 33.5% and 20.4%, respectively. Overall, multiple-dose administration of 450 and 900 mg CVC with a high-fat meal and coadministration with single dose of ritonavir 100 mg was safe and well tolerated.

The PK, safety, and tolerability of CVC were assessed in several drug-drug interaction studies. In clinical studies, potent cytochrome P450 (CYP)3A4 inhibitors such as ritonavir, darunavir/ritonavir combination, and atazanavir/ritonavir combination increased the exposure of CVC by 3.55-fold, 3.13-fold, and 3.89-fold, respectively. The exposure of midazolam, a substrate of CYP3A4, is increased by 1.84-fold when coadministered with 150 mg CVC. CVC increased the exposure of rosuvastatin (breast cancer resistance protein [BCRP] substrate) by 3.52-fold, atorvastatin and simvastatin (CYP3A4 substrates) by 1.37-fold and 2.48-fold, respectively. However, no significant increase in the exposure of digoxin (P-glycoprotein [P-gp] substrate) and caffeine (CYP1A2 substrate) was observed (Study 652-124).

Based on clinical data as well as in vitro drug interaction studies, potent CYP3A4 inhibitors could significantly increase CVC exposure. Since CYP2C8 is identified to contribute to metabolism of CVC, potent CYP2C8 inhibitors may increase exposure of CVC. CVC was identified as a P-gp substrate in vitro; however, based on currently available exposure-safety CVC data (Study 3152-107-002), coadministration of CVC with P-gp inhibitors is not expected to result in any clinically meaningful increase in CVC exposure. CVC can be coadministered with P-gp substrates such as digoxin. Caution is recommended while coadministering substrates of CYP3A4 with narrow therapeutic index (eg, midazolam). It is also recommended not to exceed the suggested maximum daily dose of rosuvastatin (BCRP substrate) and other statins (atorvastatin, lovastatin, pravastatin and simvastatin). The detailed list of disallowed medications and the list of medications that are allowed but with specific restrictions are provided in Appendix 20.4.

5.3.2. *Phase 1 Pharmacokinetic Study in Subjects with Hepatic Impairment*

A Phase 1 open-label study (Study 121 [652-1-121]) in subjects with hepatic impairment was conducted. This study was designed to evaluate the PK, safety, and tolerability of CVC in subjects with mild and moderate hepatic impairment (Child Pugh A and B) compared with matched subjects with normal hepatic function. CVC exposures were not increased in subjects with mild hepatic impairment relative to matched healthy control subjects. Cenicriviroc exposures were increased in subjects with moderate hepatic impairment relative to matched healthy control subjects. On Day 14, subjects with moderate hepatic impairment had CVC exposures approximately 29% (maximum plasma concentration [C_{max}]) to 55% (area under the concentration time curve to the last measurable concentration [AUC_{0-tau}]) higher compared with healthy matched controls. In subjects with hepatic impairment, a longer half-life was observed compared with healthy control subjects with normal hepatic function (Day 14, $t_{1/2}$ geometric mean: 37.6 hours [moderate] and 29.7 hours [mild] vs 22.4 hours [matched healthy controls, moderate] and 22.0 hours [matched healthy controls, mild]). Based on the magnitude of these observed differences in exposure in subjects with

mild or moderate hepatic impairment, it is unlikely that a CVC dose adjustment will be required.

In Study 121, CVC showed a favorable safety profile with few treatment-related AEs and with only 1 AE (mild vomiting; mild hepatic impairment subject) leading to treatment discontinuation. Two subjects (both with long-standing history of hepatitis C and liver cirrhosis) experienced Grade 3 (5.1 to 10.0 × upper limit of normal [ULN]) or Grade 4 (> 10.0 × ULN) elevations in liver transaminases during the study; however, these returned to their prior grade of severity, and both subjects completed the 14-day dosing period and all study visits with no further sequelae. Both of these subjects had bilirubin levels within normal limits.

5.3.3. *Phase 2b Study in Subjects with NASH and Liver Fibrosis*

The Phase 2b study (CENTAUR; Study 652-2-203) was a randomized, double-blind, placebo-controlled, multinational 2-year study. The study was designed to determine the efficacy and safety of CVC for the treatment of NASH in adult subjects with liver fibrosis. The study population included subjects with a nonalcoholic fatty liver disease activity score (NAS) ≥ 4 and liver fibrosis Stage 1 to 3 based on the NASH Clinical Research Network (CRN) criteria who were at increased risk of disease progression due to the presence of T2DM, body mass index (BMI) > 25 kg/m^2, and meeting at least 1 of the criteria for metabolic syndrome, or bridging fibrosis (NASH CRN Stage 3) and/or definite NASH (NAS ≥ 5). Subjects were randomized in a 2:1:1 ratio to receive 1 of 3 treatments as follows:

- CVC 150 mg once daily for 2 years (Arm A; CVC/CVC group)
- Placebo once daily for 1 year followed by CVC 150 mg once daily for an additional 1 year (Arm B; placebo/CVC group)
- Placebo once daily for 2 years (Arm C; placebo/placebo group)

Fibrosis stage, NASH status, and NAS were assessed in serial liver biopsies read by a central pathologist at baseline, Year 1, and Year 2. The central pathologist remained blinded to individual subject treatment assignment throughout the conduct of the study.

A total of 289 subjects (intent-to-treat [ITT] population) were randomized into the CENTAUR study.[21] Overall, 39 of 289 subjects (13.5%) withdrew early during Year 1 (Treatment Period 1), with the most commonly reported reasons for early discontinuation during Year 1 being due to AEs and withdrawal of consent. A total of 250 subjects (86.5%) completed Year 1 and 242 subjects (83.7%) entered Year 2 (Treatment Period 2). During Year 2, 16 subjects (5.5%) withdrew early, with the most commonly reported reason for early discontinuation during Year 2 being due to AEs, which were more commonly reported in the CVC/CVC group (3.4%, 5 subjects) compared with the placebo/CVC group (1.4%, 1 subject) and the placebo/placebo group (0 subjects).

Overall, 47.4% (137/289) of subjects were male and 52.6% (152/289) were female. Most subjects were white (86.5% [250/289]) and not Hispanic or Latino (82.4% [238/289]). The mean age at screening was 54.1 years. Except for documented evidence of T2DM, the

treatment groups were well balanced with respect to demographics and baseline characteristics. A higher percentage of subjects in the CVC/CVC group (58.6%) and placebo/CVC group (52.8%) than in the placebo/placebo group (40.3%) had documented evidence of T2DM.

Efficacy Results at Year 1

In the ITT population, 23 (15.9%) subjects in the CVC group achieved the primary efficacy endpoint (defined as a decrease in NAS by ≥ 2 points with at least a 1-point reduction in either lobular inflammation or hepatocellular ballooning AND no worsening of fibrosis stage at Year 1 relative to the Screening biopsy), compared with 27 (18.8%) subjects in the placebo group (p=0.5194, odds ratio [OR]: 0.8, 95% confidence interval [CI]: 0.44 - 1.52).

Although a statistically significant difference between the CVC and combined placebo groups was not achieved for the primary endpoint at Year 1, analyses of the key secondary endpoints (the composite summation [S1] of the 2 key secondary endpoints, "complete resolution of steatohepatitis and no concurrent worsening of fibrosis stage [S2]" and "improvement in fibrosis and no worsening of steatohepatitis [S3]") were conducted as prespecified and presented for full disclosure of data. Results for the key secondary efficacy endpoints using the ITT population are summarized in Table 2, and briefly were as follows:

- A higher proportion of subjects in the CVC group (Arm A) (7 subjects, 4.8%) than in the placebo group (Arms B+C) (4 subjects, 2.8%) achieved the composite summation (S1) of the 2 key secondary endpoints (S2+S3) at Year 1.
- A similar proportion of subjects receiving CVC or placebo achieved S2 at Year 1.
- Twice as many subjects in CVC group (Arm A) than in the placebo group (Arms B+C) achieved S3 at Year 1.
- In the subgroup of subjects with higher fibrosis stage and disease activity (ie, ITT population Year 1 excluding subjects with baseline NASH CRN Stage 1 fibrosis) at baseline, a higher proportion of subjects in CVC group (Arm A) compared with the placebo group (Arms B+C) showed improvement in fibrosis by ≥ 1 stage (NASH CRN) and no worsening of steatohepatitis (S3) at Year 1. Also, a higher proportion of subjects in CVC group (Arm A) (8 subjects, 8.2%) compared with the placebo group (Arms B+C) (3 subjects, 3.1%) had a ≥ 2 stage improvement in fibrosis AND no worsening of steatohepatitis at Year 1.

Table 5-1 CENTAUR Study: Effect of 1 Year of Treatment with CVC Versus Placebo on Fibrosis Endpoints (Year 1 Data)

	Number of Subjects (%)		
Analysis Population Endpoint/Statistic	**CVC/CVC (Arm A) (n = 145)**	**Placebo/CVC (Arm B) + Placebo/Placebo (Arm C) (n = 144)**	**Odds Ratio (95% CI) p-value**
ITT Population Year 1			
Primary endpoint: hepatic histological improvement in NAS by ≥ 2 points with at least 1-point reduction in either lobular inflammation or hepatocellular ballooning and no concurrent worsening of fibrosis at Year 1	23 (15.9)	27 (18.8)	0.816 (0.439, 1.516) p = 0.5194[a]
S1: summation of key secondary endpoints S2 and S3	7 (4.8)	4 (2.8)	1.934 (1.035, 3.614) p = 0.0388[b]
S2: complete resolution of steatohepatitis and no concurrent worsening of fibrosis stage	11 (7.6)	8 (5.6)	1.396 (0.537, 3.628) p = 0.4941[b]
S3: improvement in fibrosis by ≥ 1 stage (NASH CRN) AND no worsening of steatohepatitis	29 (20.0)	15 (10.4)	2.201 (1.113, 4.352) p = 0.0234[b]
ITT Population Excluding Subjects with Baseline NASH CRN Fibrosis Stage 1	**(n = 98)**	**(n = 96)**	
S3: improvement in fibrosis by ≥ 1 stage (NASH CRN) AND no worsening of steatohepatitis	23 (23.5)	13 (13.5)	p = 0.0708[d]
Improvement in fibrosis stage by ≥ 2 stages AND no worsening of steatohepatitis	8 (8.2)	3 (3.1)	p = 0.1237[e]

CRN = Clinical Research Network; CVC = cenicriviroc

[a] Two-sided p-value < 0.05 indicates statistical significance of the study primary endpoint.

[b] The odds ratio, 95% CI, and p-value was from ordinal logistic regression models with factors for randomized treatment group, NAS at screening (4 or ≥ 5), and fibrosis stage (≤ 2 or > 2). Two-sided p-value < 0.05 indicated statistical significance of the secondary endpoint. S1 was tested first and if significant, testing for S2 and S3 were also to be performed at a 0.05 level of significance.

[c] The p-values for S2 and S3 were from the logistic regression analysis with adjustment for the randomization strata

[d] P-values are from a CMH test with adjustment for NAS at baseline (4 or ≥ 5) and fibrosis stage at baseline (≤ 2 or > 2). Two-sided p-value < 0.05 indicated statistical significance of the secondary endpoint. S1 was tested first and if significant, testing for S2 and S3 were also to be performed at a 0.05 level of significance.

[e] P-values are from a CMH test with adjustment for NAS at baseline (4 or ≥ 5) and fibrosis stage at baseline (≤ 2 or > 2).

Efficacy Results at Year 2

Overall, the results from the final Year 2 analysis supported the clinically meaningful antifibrotic effect of CVC treatment observed in the Year 1 primary analysis. Improvement in fibrosis AND no worsening of steatohepatitis were re-assessed in a prespecified analysis among Year 1 placebo nonresponder subjects who received CVC (Arm B; placebo/CVC group) as compared with those who continued to receive placebo in Arm C from Year 1 to Year 2, which was therefore independent of the Year 1 primary analysis. Year 1 placebo nonresponders were defined as ITT subjects who were randomized to receive placebo during Year 1, did not achieve a ≥ 1-stage improvement in fibrosis AND no worsening of steatohepatitis) at Year 1, and were in the Phase 3 Eligible subgroup (ie, subjects with a diagnosis of NASH and NASH CRN fibrosis Stage of 2 or 3 assessed on the Year 1 biopsy).

Results of the analysis showed that a higher proportion of Year 1 placebo nonresponder subjects who received CVC (Arm B, placebo/CVC group) (24.4%, 10/41 subjects) experienced an improvement in fibrosis by ≥ 1 stage AND no worsening of steatohepatitis compared with subjects who remained on placebo (Arm C, placebo/placebo group) (17.1%, 6/35 subjects) from Year 1 to Year 2. Similarly, improvement in fibrosis by ≥ 1 stage regardless of effect on steatohepatitis was reported in 39.0% of placebo/CVC subjects (Arm B) versus 28.6% of placebo/placebo subjects (Arm C).

A similar and consistent antifibrotic response was observed in the pooled analysis of subjects treated with CVC for 1 year (subjects in Arm A who received CVC during Year 1 and Arm B group who received CVC during Year 2) (19.9%, 41/206 subjects) compared with subjects treated with placebo for 1 year (Arm C; data from Year 1) (11.1%, 8/72 subjects).

At Year 2, a similar proportion of subjects in the CVC/CVC (Arm A) and placebo/placebo (Arm C) groups achieved improvement in fibrosis stage by ≥1 stage AND no worsening of steatohepatitis (12.8% [15/117] versus 14.0% [8/57], respectively). Results were similar using the modified intent-to-treat (mITT) population. Similar to the overall ITT population, in the subgroup of subjects with Stage 2 or 3 fibrosis at baseline, a similar proportion of subjects in Arm A and Arm C achieved improvement in fibrosis stage by ≥1 stage AND no worsening of steatohepatitis (18.7% and 18.9%, respectively).

However, in the subgroup of subjects with fibrosis Stage 2 or 3 at baseline (ie, including only subjects who could improve by 2 or more stages), a greater proportion of subjects receiving CVC achieved a ≥ 2-stage improvement in fibrosis AND no worsening of steatohepatitis at Year 2 relative to subjects receiving placebo (9.3% [7/75] in the CVC/CVC group [Arm A] versus 2.7% [1/37] in the placebo/placebo group [Arm C], from baseline to Year 2). When only subjects with Stage 3 fibrosis were included in the analysis, 14.0% (6/43) of subjects receiving CVC versus 4.2% (1/24) of subjects receiving placebo achieved a ≥ 2-stage improvement in fibrosis AND no worsening of steatohepatitis at Year 2.

To determine the durability of histological improvement over 2 years, improvement in fibrosis by ≥ 1 stage (regardless of steatohepatitis status) was assessed in subjects with available biopsy results at all 3 timepoints (baseline, Year 1, and Year 2 [mITT Population, Year 2]). Results from this analysis showed that the proportion of CVC/CVC-treated subjects

in Arm A who achieved improvement in fibrosis by ≥ 1 stage at the end of Year 1 and maintained this antifibrotic effect at Year 2 was twice the number of placebo/placebo-treated subjects in Arm C (60% [18/30] vs 30% [3/10], respectively). Notably, 86% (12/14) of subjects in the CVC/CVC group (Arm A) with Stage 3 fibrosis at baseline that improved by at least 1 stage at Year 1 maintained the improvement in fibrosis stage (antifibrotic benefit) at Year 2 compared with 60% (3/5) subjects in the placebo/placebo group (Arm C). It is worth noting that, of 36 responders in the CVC/CVC group (Arm A) at Year 1, 6 had missing Year 2 biopsy data including 4 subjects who were CRN Stage 3 at baseline.

The placebo/placebo group showed substantial variability in the change in fibrosis from baseline to Year 1 and to Year 2, which was not readily apparent when simply measuring the proportion of placebo responders at each time point. In fact, most placebo-treated subjects who improved by ≥ 1 stage at Year 1 relative to baseline subsequently worsened from Year 1 to Year 2. Similarly, the majority of placebo-treated subjects who worsened by ≥ 1 stage at Year 1 relative to baseline subsequently improved from Year 1 to Year 2. These findings potentially reflect the fluctuations in histological features of steatohepatitis and liver fibrosis over the course of the disease and likely represent the natural history of NASH.

Collectively, the results from the Year 1 primary analysis and Year 2 final analysis demonstrate the antifibrotic effects associated with CVC treatment in adults with NASH and liver fibrosis. Although there was no apparent effect of CVC on steatohepatitis, CVC-treated subjects were more likely to achieve fibrosis improvement by at least 1 stage (following 1 year of treatment) or 2 stages (observed following 1 and 2 years of treatment) and experience a sustained antifibrotic response as assessed by 3 serial biopsies conducted at yearly intervals over a 2-year period.

Safety

The safety profile over 1 year of treatment (Treatment Period 1) was analyzed at Year 1 for subjects receiving CVC (CVC Arm A) compared with subjects receiving placebo (placebo Arms B+C). The safety profile over 2 years of treatment (Treatment Periods 1 and 2) was analyzed at Year 2 for subjects who received at least 1 dose of study drug during Year 2 (Safety Analysis Set Year 2). Results from both analyses are presented herein.

Safety Results at Year 1

The overall incidence of treatment-emergent adverse events (TEAEs) during Treatment Period 1 was similar between subjects in the CVC Arm A and placebo Arms B+C (93.1% vs 92.4%, respectively). The incidence of study drug-related AEs was 41.7% in the CVC Arm A and 37.5% in placebo Arms B+C. No subjects died during Treatment Period 1. Seventeen subjects (11.8%) in the CVC Arm A and 11 subjects (7.6%) in placebo Arms B+C experienced a serious adverse event (SAE); only 1 SAE of Grade 2 arrhythmia was deemed related to study drug, which resolved while the subject remained on blinded study drug. Overall, 7.6% of subjects discontinued study drug due to an AE (CVC, 6.3% of subjects; placebo, 9.0% of subjects).

Overall, the most commonly reported TEAEs regardless of causality were diarrhea (51 subjects, 17.7%), headache (43 subjects, 14.9%), nausea (33 subjects, 11.5%), fatigue (38 subjects, 13.2%), and abdominal pain upper (33 subjects, 11.5%). The most notable differences for AEs reported in ≥ 10% of subjects in any group were: diarrhea, nausea, and arthralgia, reported more commonly in CVC Arm A compared with placebo Arms B+C (20.8% vs 14.6%; 17.4% vs 9.0%; and 12.5% vs 4.2% of subjects, respectively); abdominal pain upper and back pain, reported less commonly in CVC Arm A than in placebo Arms B+C (9.7% vs 13.2%; 7.6% vs11.8% of subjects, respectively).

The most commonly reported study drug-related AEs in CVC Arm A were diarrhea (9.0% of subjects), nausea (8.3% of subjects), and flatulence (4.9% of subjects). The most commonly reported study drug-related AEs in placebo Arms B+C were headache (7.6% of subjects), fatigue (4.2% of subjects), and ALT increased (3.5% of subjects). The most frequently reported study drug-related clinical TEAEs of at least moderate (Grade 2) severity occurring in ≥ 2% of subjects in any treatment group were fatigue (2.8%) and diarrhea (2.1%) in CVC Arm A and headache (3.5%) in placebo Arms B+C.

The incidence of Grade 3 or 4 AEs was similar between CVC Arm A and placebo Arms B+C (26.4% vs 25.7% of subjects). The most commonly reported Grade 3 or 4 AEs in CVC Arm A were ALT increased (6.3% of subjects), AST increased (2.8% of subjects), gamma-glutamyl transferase (GGT) increased (2.8% of subjects), arthralgia (2.8% of subjects), and back pain (2.1% of subjects). The most commonly reported Grade 3 or 4 AEs in placebo Arms B+C were ALT increased (6.3% of subjects), arthralgia (2.1% of subjects), and back pain (2.1% of subjects). A total of 3 Grade 3- 4 TEAEs of hepatobiliary disorders were reported during Year 1: 1 AE of autoimmune hepatitis and 1 AE of cholelithiasis in CVC Arm A and 1 AE of autoimmune hepatitis in placebo Arms B+C. A greater number of participants in CVC Arm A (22.2%) experienced treatment-related TEAEs of at least Grade 2 severity than in the placebo Arms B+C (13.9%). The most frequently reported study drug-related clinical TEAEs in any treatment group were fatigue (2.8%) and diarrhea (2.1%) in the CVC Arm A and headache (3.5%) in the placebo Arms B+C.

The incidence of treatment-emergent Grade 3 or 4 laboratory abnormalities was generally similar between groups. Grade 4 uric acid elevations, which occurred in subjects with increased baseline values, and asymptomatic Grade 3 amylase elevations were observed more frequently in the CVC Arm A than the placebo Arms B+C (7.6% vs 4.2% and 4.2% vs 0.7%, respectively). During Year 1, 9.7% of subjects (14/144) in CVC Arm A and 7.6% of subjects (11/144) in placebo Arms B+C met protocol-defined biochemical criteria for suspected drug-induced liver injury (DILI).

Safety Results at Year 2

The mean duration of exposure was comparable across all treatment groups in the safety analysis set for Year 2 (694.0, 713.3, and 708.7 days for the CVC/CVC [Arm A], placebo/CVC [Arm B], and placebo/placebo [Arm C] groups, respectively).

For subjects who received at least 1 dose of study drug in Year 2 (N = 242), the safety profile of CVC 150 mg in subjects treated daily with CVC for 1 (placebo/CVC group) or 2 years

(CVC/CVC group) was comparable to that observed in subjects treated with placebo (placebo/placebo) and consistent with that reported after 1 year of CVC treatment.[21] The overall incidence of TEAEs during the study was similar across the treatment groups (≥ 75.0% of subjects in each group). Overall (N = 242), the 3 most frequently reported AEs regardless of causality were nasopharyngitis (7.4%, 18 subjects), upper respiratory tract infection (6.6%, 16 subjects), fatigue (6.6%, 16 subjects). The following TEAEs were experienced more frequently in CVC Arm A than placebo Arm C: nasopharyngitis (9.1% versus 3.3%), upper respiratory tract infection (6.6% versus 5.0%), urinary tract infection (7.4% versus 0), nausea (5.8% versus 3.3%), arthralgia (5.0% versus 3.3%), fatigue (9.1% versus 5.0%), ALT increased (5.0% versus 3.3%), cough (5.0% versus 0).

Fewer treatment-related TEAEs were reported overall in Treatment Period 2 than in Treatment Period 1; 34/242 (14.0%) subjects versus 114/288 (39.6%), respectively. The number of subjects in the CVC/CVC group (Arm A) (15.7%) who experienced treatment-related TEAEs was comparable to that reported in placebo/placebo group (Arm C) (15.0%) and lower in placebo/CVC group (Arm B) (9.8%). A greater number of subjects in CVC/CVC group (Arm A) (8.3%) experienced treatment-related TEAEs of at least Grade 2 severity than in the placebo/placebo group (Arm C) (5.0%). The most frequently reported study treatment-related TEAE in any treatment group was fatigue (3.3%) in the CVC/CVC group (Arm A) and ALT increased (3.3%) in the placebo/placebo group (Arm C). This was consistent with that reported after 1 year of treatment. [21]

Overall, the number of participants in the CVC/CVC group (Arm A) (14.9%) who experienced Grade 3-4 TEAEs, regardless of causality, was comparable to that reported in the placebo/placebo group (Arm C) (15.0%) during Treatment Period 2. The most frequently reported Grade 3-4 TEAE for both the CVC/CVC and placebo/placebo groups was ALT increased (2.5% in CVC/CVC [Arm A] and 3.3% in placebo/placebo [Arm C]).

No deaths occurred during the study. Through 2 years of the study, 10.3% (25/242) of subjects had at least 1 SAE (Safety Analysis Set for Year 2). No other SAE occurred in > 1 subject except osteoarthritis (2 subjects in CVC/CVC [Arm A]). Overall, 6 of 242 (2.5%) subjects withdrew study drug due to a TEAE, including 3 subjects due to increased ALT, 1 subject due to nausea, and 1 subject due to diverticulitis in the CVC/CVC group (Arm A), and 1 subject with abdominal discomfort in the placebo/CVC group (Arm B).

Of the subjects who received at least 1 dose of study drug during Year 2, 4.1% of subjects in CVC/CVC group (Arm A) experienced an AE leading to discontinuation, while no subjects in the placebo/placebo group (Arm C) discontinued due to an AE. The only AE leading to discontinuation, regardless of causality, reported in at least 2 subjects in CVC/CVC group (Arm A) was ALT increased (3 subjects, 2.5%); all were Grade 3 severity. For subjects who crossed over after 1 year of placebo treatment to CVC treatment, only 1 subject experienced an AE leading to discontinuation (abdominal discomfort) after crossing over.

The incidence of treatment-emergent Grade 3 or 4 laboratory abnormalities during Year 2 was generally similar across the treatment groups. In total, 3.3% (4/121) subjects in CVC/CVC group (Arm A), 3.3% (2/61) subjects in the placebo/CVC group (Arm B), and 1.7% (1/60) subjects in the placebo/placebo group (Arm C) met any protocol-defined

biochemical criterion for suspected DILI. Hepatobiliary disorders during Treatment Period 2 were reported in 5/242 (2.1%) subjects overall. Of note, among the subjects who met the criterion for suspected DILI during Year 1, 2 hepatobiliary AEs of "autoimmune hepatitis" were reported during Year 1 (1 subject in CVC Arm A group [Grade 3] and 1 subject in the placebo Arms B+C [Grade 3]), and these subjects did not continue treatment during Year 2. One additional subject in the CVC group (Arm A) had a postbaseline liver biopsy "suggestive of autoimmune hepatitis or a drug hepatoxicity mimicking autoimmune hepatitis," which was performed in the context of treatment-emergent Grade 3 elevations in liver transaminases.

No meaningful changes in vital signs, ECGs, or anthropometric parameters were observed.

Pharmacokinetics/Pharmacodynamics

Findings from the pharmacokinetic/pharmacodynamic (PK/PD) Year 1 efficacy analyses of CENTAUR were consistent with those of previous studies, which served as the basis for selection of the CVC dose of 150 mg evaluated in this study. In CENTAUR, the CVC dose of 150 mg daily provided > 77% of subjects being exposed to minimum plasma concentration (C_{min}) values that exceed the C_{min} associated with half-maximal response ($EC_{min}50$; most conservative $EC_{min}50$ of 50 ng/mL, based on data from the HIV Phase 2 program), providing an expectation of substantial and near maximal antagonism of CCR2/CCR5 in most subjects at this dose. When using the $EC_{min}50$ of 40 ng/mL, which was based on changes in CCL2 and CCL4 levels (ie, reciprocal increases in CCL2 and CCL4 levels observed due to effective CCR2 and CCR5 blockade by CVC) observed in the CENTAUR study, > 84% of CVC-treated subjects achieved this target concentration.

Results from a drug interaction study (Study 652-123) have shown that administration of a proton pump inhibitor (PPI) 90 minutes prior to CVC, dosed at 150 mg, resulted in significantly decreased CVC concentrations. In the CENTAUR study, PPIs were allowed with specific dosing instructions (ie, dosing of PPIs at least 2 hours after CVC 150 mg daily dose) and were used in 44% of all subjects. Although fewer subjects achieved an $EC_{min}50$ of 40 ng/mL when using PPIs (84.5%) compared with those who did not (94.3%), a similar proportion of subjects in both groups achieved the key efficacy endpoint of improvement in fibrosis by at least 1 stage AND no worsening of steatohepatitis: 21.0% for PPI users versus 25.0% for nonusers, respectively (mITT). Therefore, the dose of 150 mg appears sufficient when managing coadministration of CVC with commonly used concomitant medications, such as PPIs.

Taken together, along with the lack of apparent exposure-response for efficacy in this study, the main findings from the PK/PD analyses further support that the CVC 150 mg dose was able to maximize CCR2/CCR5 blockade in most subjects and support its evaluation in the Phase 3 program.

5.4. Study Rationale

The clinically important results from the Phase 2b CENTAUR study are robust and suggest that CVC treatment may be disease modifying in adult patients with liver fibrosis as a result

of NASH, particularly when considering the comprehensive and clinically relevant evidence which demonstrates that liver fibrosis, regardless of other histological components of steatohepatitis, is the only histologic feature independently associated with all-cause mortality and liver-related outcomes in patients with NAFLD.[22] Cenicriviroc appears to be safe with no notable differences observed in previous clinical studies in the incidence of TEAEs and laboratory abnormalities, including liver transaminase elevations, which were generally similar between treatment groups. Safety findings in CENTAUR were consistent with that of the extensive clinical experience with CVC.

The open-label rollover protocol will be conducted to offer continued access to CVC to subjects who completed the CENTAUR study, progressed to cirrhosis, or reached an adjudicated liver-related clinical outcome and completed the AURORA study. In addition, this study will evaluate the safety and tolerability of CVC with long-term treatment.

5.5. Dose Rationale

A dose of CVC 150 mg will be evaluated for the treatment of liver fibrosis in adult subjects with NASH in the open label rollover study.

This dose was evaluated in the CENTAUR study (652-2-203) and selected based on the clinical activity, PK, PD, and safety data from prior studies (652-1-110, 652-1-111, 652-120, 652-1-121, 652-1-122, 652-123, 652-124, 652-2-202, and 652-2-201), which together support:

- Evidence of meaningful clinical efficacy of CVC 150 mg in subjects with NASH and liver fibrosis in the CENTAUR study (Study 652-2-203)
- Evidence that CVC 150 mg is safe and well tolerated subjects with NASH and liver fibrosis in the CENTAUR study (Study 652-2-203)
- CVC dose of 150 mg provides an expectation of effective primary pharmacology (ie, CCR2 and CCR5 antagonism)
- Evidence of improvement in systemic inflammation biomarkers support underlying CVC pharmacology, and
- The dose of 150 mg appears sufficient when managing coadministration of CVC with commonly used concomitant medications, such as PPIs.

6. STUDY OBJECTIVES

Primary Objective:

The primary objective of this study is to provide open-label treatment with CVC to subjects who have previously participated in CVC studies.

Secondary Objective:

The secondary objective of this study is to assess the long-term safety of continued treatment with CVC for subjects who have previously participated in CVC studies.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a Phase 2, open-label, multi-center, study (up to approximately 480 centers) to provide open-label CVC to subjects with liver fibrosis in the treatment of nonalcoholic steatohepatitis.

Subjects from the following studies will be eligible to receive open-label CVC 150 mg once daily:

- Subjects who have completed both Treatment Period 1 and Treatment Period 2 (Year 1 and Year 2) of the CENTAUR study (652-2-203), regardless of their treatment assignment in the CENTAUR study (CVC or placebo).
- Subjects who have completed the AURORA study (3152-301-002) as a result of progression to cirrhosis or reaching an adjudicated liver-related clinical outcome in either Part 1 or Part 2 of the study, regardless of their treatment assignment (CVC or placebo). Refer to Section 8.2 for additional details.

Subjects will be required to rollover to this continued access study within 1 month of completing their final visit assessments in either the CENTAUR or AURORA study. Eligible subjects who-completed these studies, prior to initiation of this protocol at their study center, will be allowed to participate in this rollover study.

Subjects will undergo study visits for safety assessments at the start of this continued access study (Baseline), then every 3 months for the duration of the study, or at the discretion of the investigator. A central laboratory will be used for laboratory assessments, including any deemed necessary by the investigator; all other study assessments will be conducted locally.

This is a rollover study in which CVC treatment will continue to be provided until it is commercially available or if development is terminated, as applicable.

The study design is illustrated in Figure 7-1.

Figure 7-1 Study Design Schematic

Open-Label Period CVC 150 mg once daily		**Safety Follow-up**
Year 1	**Year 2; and ongoing**	1-month Follow-up
Baseline Day 1[a]	Months 3, 6, 9, 12, 15, 18, 21, 24[b]	

a Subjects completing Treatment Periods 1 and 2 of the CENTAUR study or completing the AURORA study as a result of progression to cirrhosis or reaching an adjudicated liver-related clinical outcome in either Part 1 or Part 2 of the study, regardless of their treatment assignment (CVC or placebo), must provide informed consent to Study 3152-201-002 before receiving open label CVC. Subjects are required to rollover to Study 3152-201-002 within 1 month of completing their final visit assessments in either the CENTAUR or AURORA study. Subjects who-completed the CENTAUR or the AURORA study, prior to initiation of this protocol at their study center, will be allowed to participate in this rollover study.

b Subjects will continue to be seen every 3 months until CVC becomes commercially available or if development is terminated, as applicable.

8. STUDY POPULATION

8.1. Number of Subjects

It is expected that a total of approximately 560 subjects may rollover from both the CENTAUR study (652-2-203) and AURORA study (3152-301-002) (refer to Section 7.1).

8.2. Inclusion Criteria

For a subject to be eligible for participation in this study, *all* of the following criteria must apply.

1. Subjects who have either:

   - Completed both Treatment Period 1 and Treatment Period 2 (Year 1 and Year 2) of the CENTAUR study (652-2-203), including a Year 2 liver biopsy
   - Completed the AURORA study and who reached an adjudicated liver-related clinical outcome in Part 1 or Part 2 of the study of:
     - Histopathologic progression to cirrhosis
     - MELD score ≥ 15
     - Ascites (requiring intervention, ie, large volume paracentesis ≥ 1L or initiation of a diuretic)
     - Hospitalization (as defined by a stay of ≥ 24 hours) for onset of: variceal bleed, hepatic encephalopathy (defined by a West Haven Stage of ≥ 2), spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis with positive ascitic fluid bacterial culture)

2. Has been determined to be in a stable medical condition (minimum of approximately 3 months from the date of the clinical event in AURORA to the Baseline Visit of this study) based on medical history or physical examination, in the opinion of investigator. Inclusion criterion applies only to subjects coming from the AURORA study (3152-301-002).

[redacted]

[redacted]

8.3. Exclusion Criteria

A subject will not be eligible for participation in this study if *any* of the following criteria apply.

1. [redacted]
2. Prior or planned liver transplantation
3. Other known causes of chronic liver disease, such as the following:
    - Alcoholic liver disease
    - Primary biliary cirrhosis
    - Primary sclerosing cholangitis
    - Autoimmune hepatitis
    - Wilson's disease, hemochromatosis, or iron overload
    - Alpha-1 antitrypsin (A1AT) deficiency

[redacted]

9. TREATMENTS

9.1. Treatments Administered

Eligible subjects will receive open-label CVC 150 mg, 1 tablet administered orally once daily with food.

9.2. Study Drug

9.2.1. *Investigational Product*

Chemical Name:	(*S*)-8-[4-(2-Butoxyethoxy)phenyl]-1-isobutyl-*N*-(4-{[(1-propyl-*1H*-imidazol-5-yl)methyl]sulfinyl}phenyl)-1,2,3,4-tetrahydro-1-benzazocine-5-carboxamide monomethane sulfonate
Generic Name:	Cenicriviroc mesylate
Abbreviated Name:	CVC
Laboratory Designation:	TBR-652
Trade Name:	Not applicable

The CVC drug product is formulated with fumaric acid (160 mg) and other excipients, including microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and Opadry® II yellow (film coating).

The CVC drug product is provided as 150-mg yellow-coated, immediate release tablets for oral administration.

9.2.2. *Packaging and Labeling*

The study drug will be supplied, as described above, by Sponsor and will be packaged in high-density polyethylene (HDPE) bottles containing desiccant, and induction sealed. The site pharmacist, investigator, or designee will dispense study drugs. Dispensed supplies will contain sufficient drug to cover the visit window period (± 2 weeks).

All labels for CVC will meet all applicable requirements of the United States (US) Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices and/or all local regulations, as applicable.

9.2.3. *Storage*

All study drug should be stored at controlled room temperature (refer to the packaging or study/pharmacy manual). CVC tablets will continue to be monitored for stability at ICH recommended storage conditions.

9.2.4. *Study Drug Dispensing and Collection*

Study drug will be supplied in a bottle containing medication for each subject, which is sufficient for a monthly dosing supply. [redacted]

Subjects will be instructed that 1 tablet of study drug must be taken once daily with food.

[redacted]

9.2.5. ***Investigational Product Accountability***

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and must be readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug. The investigator or designee must maintain records that document the following:

- Study drug delivery to the study site
- Inventory at the site
- Storage conditions
- Use by each subject, including tablet counts from each supply dispensed
- Return of study drug to the investigator or designee.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the study drug and study subjects.

The study drug must be used only in accordance with the protocol. The investigator will also maintain records adequately documenting that the subjects were provided the study drug specified.

Completed accountability records will be archived by the site. Guidance and information regarding the final disposition of all study drug are provided in the Pharmacy Manual.

9.3. Randomization

This is an open-label study; no randomization procedures will be performed. Subjects will retain their subject identification number from either the CENTAUR study or AURORA study.

9.4. Study Drug Administration

Subjects will take 1 tablet of open-label CVC daily for the duration of the study or upon study discontinuation.

Subjects will be instructed that 1 tablet of study drug must be taken once daily with food. Subjects will bring their study drug bottle to the clinic for drug accountability.

If a subject has missed a dose of study drug and is still within 12 hours of the time it is usually taken, the subject should take a dose of the missed drug as soon as possible, with food. The subject may then continue the usual dosing schedule. If the subject has missed a

dose of a study drug more than 12 hours after the time it is usually taken, subject should not take the missed dose and simply resume the usual dosing schedule. The subject should not take a double dose to make up for a missed dose or take more than 1 tablet within 12 hours.

9.5. Blinding

No blinding is planned for this open-label study.

9.6. Prior and Concomitant Therapy

A prior medication is defined as a (nonstudy) medication taken at any time during 30 days before first study drug intake and stopped before the date of first dose of study drug. Any prior medication received within 30 days before the first dose of study drug will be recorded in the electronic case report form (eCRF).

All medications (or treatments) other than study drug taken or received by the subject at any time during the study from first intake of study drug through the 1-Month Follow-up Visit after last study drug intake (or final visit, for subjects who do not complete a Follow-up Visit) will be considered concomitant medications (or treatments). This includes medications ongoing at the time of first study drug intake and medications started after first study drug intake. A new concomitant medication will be a (nonstudy) medication started or for which the dose increased between first study drug intake through the 1-Month Follow-up Visit after last study drug intake (or final visit, for subjects who do not complete a Follow-up Visit). All concomitant medications and treatments other than study drug, taken or received at any time during the study from first intake of study drug through to the 1-Month Follow-up Visit, will be recorded in the eCRF.

A subsequent medication is defined as a (nonstudy) medication taken after the date of the 1-Month Follow-up Visit (or 30 days after last intake of study drug, if no 1-Month Follow-up Visit occurs). Any subsequent medication taken after the 1-Month Follow-up Visit (or 30 days after last intake of study drug, if no 1-Month Follow-up Visit occurs) will be recorded in the eCRF.

Subjects will be allowed to continue their usual standard-of-care medications that are not specifically excluded by the protocol. The detailed list of disallowed medications and the list of medications that are allowed but with specific restrictions are provided in Appendix 20.4.

The following classes of medications are disallowed at any time during the open-label treatment period, from Baseline through the 1-Month Follow-up Visit, if applicable:

- Potent CYP3A4 inhibitors and CYP3A4 inducers will be excluded
- Potent CYP2C8 inhibitors will be excluded
- Drugs with narrow therapeutic windows that are sensitive CYP3A4 substrates will be excluded (ie, drugs that should not be coadministered with weak CYP3A4 inhibitors such as CVC)

The disallowed concomitant medications commonly administered to patients with NASH are provided in Appendix 20.4.

Should subjects have a need to initiate treatment with any disallowed concomitant medication, the medical monitor must be consulted prior to initiation of the new medication. In instances where a disallowed medication is initiated prior to discussion with the medical monitor, the investigator must notify the Sponsor or designee as soon as he/she is aware of the use of the excluded medication to discuss the subject's continued participation in the study.

The following medications are allowed, but should be used with caution as CVC (a weak CYP3A4 inhibitor and BCRP inhibitor) may increase exposure of these CYP3A4 and BCRP substrates or these medications may affect the absorption of CVC. If used, these medications should be used at the doses recommended in Appendix 20.4. Clinical monitoring and dose titration are recommended to achieve the desired clinical response.

Lipid Lowering Agents:
Atorvastatin, simvastatin, pravastatin, and lovastatin (CYP3A4 substrates), and rosuvastatin (BCRP substrate)
Pitavastatin use is allowed without dose restriction.

Other Medications to be Used with Caution
Intravenous midazolam use is allowed at the discretion of the investigator for surgical outpatient procedures; however, if given for biopsies performed during this study, or for any procedure requiring this medication after intake of study drug, the first dose should be reduced by 50% of the recommended dose and titrated according to the desired clinical response.

Intravenous alfentanil or fentanyl are not allowed for biopsies performed during the open-label study or for any procedures requiring these medications after intake of study drug.

When required, acid-reducing agents should be administered at least 2 hours after the CVC dose to ensure that adequate CVC concentrations are maintained. When possible, use of an H_2 receptor antagonist (except cimetidine) or antacids is preferred over a PPI. It is recommended to start with the lowest dose of these agents and titrate according to clinical response.

- If H_2 receptor antagonists (eg, famotidine or ranitidine) are used, these should preferably be given from 2 to 12 hours after administration of study drug at a dose that does not exceed doses comparable to famotidine 40 mg daily.
- If antacids (eg, aluminum hydroxide, calcium carbonate, magnesium carbonate, magnesium hydroxide, or bismuth subsalicylate) are used, these should preferably be given at least 4 hours after administration of study drug due to their immediate effect in increasing gastric pH.
- If PPIs (eg, omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, or dexlansoprazole) must be utilized, these should preferably be given approximately 3 hours after administration of study drug at a dose that does not exceed doses comparable to omeprazole 20 mg daily. Due to the prolonged acid-reducing effect of

PPIs (~16 – 24 hours), it is advised to follow these dosing recommendations to reduce their potential impact on CVC absorption at subsequent dosing.

9.7. Additional Restrictions and Precautions

Subjects should refrain from strenuous physical activity (eg, weight lifting, strenuous yard work, intensive exercise workouts) for 48 hours prior to study visits and laboratory evaluations.

If a liver biopsy is required, it is allowed. However, the medical monitor must be notified of the scheduled biopsy. Data from the pathology reading of liver biopsies will be collected on the eCRF.

9.8. Treatment Adherence

Subjects will bring all of their study-supplied pill bottles to every clinic visit, and clinic staff will assess adherence based on the number of remaining pills less any overage provided to cover the visit window (± 2 weeks). Subjects who miss doses must be counseled on the importance of adhering to their daily dosing schedule.

10. STUDY PROCEDURES

Study procedures are summarized across all study visits within the Schedule of Assessments (Table 20-1).

Subjects should refrain from strenuous physical activity (eg, weight lifting, strenuous yard work, intensive exercise workouts) for 48 hours prior to study visits and laboratory evaluations.

Of note, liver biopsies are not mandated on this study. However, should a liver biopsy be conducted at the discretion of the investigator, the site must notify the medical monitor of the scheduled biopsy. Data on the liver biopsy will be collected in the eCRF. Additionally, transient elastography (TE) is not required in this study, however if assessment of liver stiffness is made via TE or liver imaging, these data will be collected in the eCRF.

10.1. Baseline

Prior to any clinical procedures and evaluations, written signed informed consent must be obtained. Subjects will be required to rollover to this continued access study and undergo Baseline Visit assessments within 1 month of completing their final visit assessments in either the CENTAUR study or AURORA study (except in the case of eligible subjects who completed these studies prior to initiation of this protocol at their study center, who will be allowed to participate in this rollover study).

At the Baseline Visit, the following procedures and assessments should be conducted:

- Informed consent
- Confirm inclusion/exclusion criteria
- Adverse events and concomitant medications
- Symptom-directed physical examination
- Medical history
- Vital signs (systolic and diastolic blood pressure, temperature, pulse rate, and respiration rate)
- Height and weight, for determination of body mass index (BMI), waist circumference and hip circumference
- Urine pregnancy test for females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test
- Blood draw for determining/obtaining the following:
    - Hematology and serum chemistry laboratory tests (see Section 11.1.2)
    - Coagulation profile, including INR (see Section 11.1.2)
    - FSH from postmenopausal women only (not required if taking hormone replacement therapy or surgically sterile)

- Blood collection for IgG, anti-SMA (smooth muscle antibodies), anti-LKM1 (liver/kidney microsome type 1), antinuclear antibody (ANA), and anti-LC1 (liver cytosol type 1)
- Plasma and serum samples for storage

- Study drug dispensation (see Section 9.2.4)

10.2. Open-label Treatment Period (Months 3, 6, 9, 12, 15, 18, 21, 24, etc., until CVC becomes commercially available or if development is discontinued, as applicable)

Subjects should return to the clinic every 3 months for general safety assessments. The following procedures and assessments are to be conducted at each of the clinic visits:

- Adverse events and concomitant medications
- Symptom-directed physical examination
- Urine pregnancy test for females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
- Blood draw for determining/obtaining the following:
  - Hematology and serum chemistry laboratory tests (see Section 11.1.2)
  - Coagulation profile, including INR (see Section 11.1.2)
  - Plasma and serum samples for storage
- Study drug accountability (see Section 9.2.5)

10.3. Discontinuation Visit

Subjects may discontinue study treatment at any time for any reason (see Section 10.6) without bias or penalty to medical care.

For subjects who discontinue study drug for any reason while the study is ongoing, every effort should be made to ensure that they return for discontinuation procedures within 48 hours after discontinuing study drug. These subjects will be required to return to the clinic 1 month after the last dose of study drug for a Follow-up Visit (see Section 10.4).

The following procedures and assessments for Discontinuation will be conducted:

- Adverse events and concomitant medications
- Symptom-directed physical examination
- Weight
- Urine pregnancy test for females of childbearing potential only (positive urine pregnancy tests will be confirmed with a serum test)
- Blood draw for determining/obtaining the following:
  - Hematology and serum chemistry laboratory tests (see Section 11.1.2)

- Coagulation profile, including INR (see Section 11.1.2)
- Plasma and serum samples for storage

- Study drug accountability (see Section 9.2.5)

10.4. 1-Month Follow-up

Subjects should undergo follow-up evaluations approximately 1 month after the last dose of study drug. Subjects who discontinue study drug will be required to return to the clinic 1 month after the last dose of study drug for a Follow-up Visit, at which time the following procedures and assessments are to be performed:

- Adverse events and concomitant medications
- Symptom-directed physical examination
- Urine pregnancy test for females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test
- Blood draw for determining/obtaining the following:
  - Hematology and serum chemistry laboratory tests (see Section 11.1.2)
  - Coagulation profile, including INR (see Section 11.1.2)
  - Plasma and serum samples sample for storage
- Study drug accountability (see Section 9.2.5)

10.5. Missed Scheduled Visits

Every attempt should be made to have subjects stay on schedule for study visits (Table 20-1).

10.6. Criteria for Discontinuation of Study Treatment

11. STUDY ASSESSMENTS

No efficacy or PK assessments are planned for this continued access study.

[redacted]

11.1. Assessments of Safety

Adverse events will be assessed at each study visit, in addition to safety laboratory parameters.

11.1.1. *Adverse Events and Serious Adverse Events*

11.1.1.1. Definitions

11.1.1.1.1. Adverse Event

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

11.1.1.1.2. Treatment-Emergent Adverse Events

An event will be considered a treatment-emergent adverse event (TEAE) if:

- The event began on or after the date of the first dose of study drug; or
- An exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition on or after the date of the first dose of study drug.

An AE that occurs more than 30 days after the last dose of study drug will not be counted as a TEAE.

11.1.1.1.3. Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as any adverse event caused by the use of a pharmaceutical product. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the pharmaceutical product caused the event.

11.1.1.1.4. Suspected Adverse Reaction

Suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that the study treatment caused the adverse event. “Reasonable possibility” means there is evidence to suggest a causal relationship between the study treatment and adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means an adverse event caused by a study treatment.

11.1.1.1.5. Unexpected Adverse Event or Reaction

An adverse event or suspected adverse drug reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

11.1.1.1.6. Events Related to Disease Under Study

Worsening of a pre-existing illness other than the disease under study will be assessed as an AE. If such an AE meets the definition of an SAE (see Section 11.1.1.1.10), it must be reported as such (see Section 11.1.1.2).

11.1.1.1.7. Clinically Significant Laboratory Abnormalities

Any laboratory abnormalities deemed clinically significant by the investigator must be reported as an AE. A clinically significant abnormality is a confirmed abnormality (by repeat testing) that is changed sufficiently from baseline so that in the judgment of the investigator a change in management is warranted. This alteration may include: monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment.

See Section 11.1.1.2 for details regarding the management and monitoring of laboratory abnormalities of interest.

11.1.1.1.8. Surgical Procedures

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of the study treatment. In the latter case, the condition should be reported as medical history.

11.1.1.1.9. Overdose

An overdose is defined as a subject's report of taking more than 1 tablet of study drug (ie, more than 1 tablet per day of CVC). Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. For reporting purposes, overdose will be considered an SAE only if any of the seriousness criteria are met (see definition in Section 11.1.1.1.10).

11.1.1.1.10. Serious Adverse Event or Serious Adverse Reaction

An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE

  - An AE or suspected AE is considered life-threatening if, in the view of either the investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization (ie, admission, overnight stay) or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical events
  - An important medical event is one that, when based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition of an SAE. (Examples of such events include allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

11.1.1.1.11. Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or nonserious) is one of scientific and medical concern specific to the Sponsor's study drug/device or program, which warrants ongoing monitoring and rapid communication by the investigator to the Sponsor. Such an event might warrant further investigation in order to characterize and understand it.

Elevations in biochemistry that are associated with liver injury have been identified as a potentially important risk and are considered AESI for the study treatment in this protocol. Biochemical criteria for suspected DILI cases are defined in Section 11.1.3.4. Cases of suspected DILI as defined by the prespecified criteria in Section 11.1.3.4 should be reported to the Sponsor within 24 hours on the AESI form (see Section 1) and will be adjudicated by a hepatologist with expertise in DILI.

11.1.1.2. Adverse Event and Clinically Significant Laboratory Abnormality Recording

Treatment-emergent adverse events and laboratory test abnormalities considered to be clinically significant should be recorded as adverse events in the CRF.

The AE or clinically significant laboratory abnormality should be reported in standard medical terminology. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. If a definitive diagnosis is not possible, the individual symptoms and signs should be recorded.

If the laboratory abnormalities are part of a clinical constellation of signs and/or symptoms that comprise a medical diagnosis, then the terminology for that medical diagnosis should be used in the adverse event record.

Adverse events and clinically significant laboratory abnormalities fall into the categories of "nonserious" and "serious." From the time of informed consent and throughout the study, all AEs and clinically significant laboratory abnormalities must be recorded in the eCRF, regardless of apparent causality from use of the study treatment.

The following information should be captured for all AEs and clinically significant laboratory abnormalities: date of onset and end date or outcome (eg, ongoing), severity of the event, seriousness of the event, investigator's opinion of the relationship to investigational product (CVC), action taken with regard to any of the study drug and treatment required for the AE, cause of the event (if known), and information regarding the resolution/outcome.

Adverse events classified as serious must be recorded on the appropriate SAE reporting tool and reported to Sponsor using expeditious handling to comply with regulatory requirements (see Section 11.1.1.5).

11.1.1.3. Adverse Event Classification

The intensity of an AE or clinically significant laboratory abnormality will be graded according to the scale below in addition to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 Table for Grading the Severity of Adult Adverse Events (see Appendix 20.2). The clinical significance of the AE is determined by the investigator. The investigator is encouraged to consult with the medical monitor.

- **Grade 1 (Mild)**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Grade 2 (Moderate)**: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- **Grade 3 (Severe)**: Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- **Grade 4 (Life-Threatening)**: Life-threatening consequences; urgent intervention indicated
- **Grade 5 (Death)**: Death related to AE

When the intensity of an AE changes over time for a reporting period (eg, between visits), each change in intensity will be reported as an AE until the event resolves. For example, 2 separate AEs will be reported if a subject experiences Grade 1 diarrhea for 3 days, meeting the definition of an AE, and then after 3 days the event increases to a Grade 3 intensity that lasts for 2 days and then resolves. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the AE definition and a stop date equal to the day that the event increased in intensity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date on the day that the event changed intensity again or resolved. For analysis purposes, this will be considered 1 AE for this subject and the maximum intensity will be recorded.

The relationship or association of the AE to a study drug should be assessed using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the investigational medicinal product. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication)
- **Yes:** A temporal relationship exists between the AE onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the study drug. In case of cessation or reduction of the dose, the AE abates or resolves and reappears upon rechallenge.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or liver biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure
- **Yes:** The adverse event occurred as a result of protocol-mandated procedures such as venipuncture.

11.1.1.4. Adverse Event Coding

AE verbatim terms provided by the investigator will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0 or later.

11.1.1.5. Reporting of Serious Adverse Events

The Sponsor is required to expedite to regulatory authorities reports of SAEs, serious ADRs, or suspected unexpected serious adverse reactions (SUSARs) in line with relevant legislation or regulations, including the applicable US FDA Code of Federal Regulations, the European Commission Clinical Trials Directive (2001/20/EC), and other country specific legislation or regulations. Expectedness of SAEs will be determined by Sponsor using reference safety information specified in the Investigator Brochure.

Any SAE, serious ADR, or SUSAR that occurs during the study from the time of signing the informed consent form (ICF) to within 1 month following discontinuation of study treatment, regardless of relationship to the study treatment, must be reported within 24 hours to the contact below:

Send completed Safety Report Forms to Global Drug Safety and Epidemiology, Allergan plc (see Section 1)

The required SAE information must be completed on the SAE Form. The Sponsor may request additional information from the investigator to ensure the timely completion of

accurate safety reports. For questions on SAE reporting, please contact the medical monitor (see Section 1 for contact information).

A copy of the submitted SAE form must be retained on file by the investigator. The investigator must submit the SAE to the IRB/IEC according to local requirements and retain documentation of these submissions in the site study file.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE Form.

If the investigator detects an SAE in a study subject after the end of the period of observation, and considers the event possibly related to prior study treatment, he/she should contact the medical monitor to determine how the event should be documented and reported.

In case of emergency, contact the medical monitor (see Section 1 for contact information).

All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the IRB/IEC as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

In accordance with the EU Clinical Trials Directive (2001/20/EC), the Sponsor or specified designee will notify worldwide regulatory authorities and the relevant Ethics Committees in concerned Member States of applicable SUSARs as individual notifications or through a periodic line listing.

11.1.1.6. Follow-up of AEs and SAEs

Adverse events (including SAEs) will be collected from the time of informed consent, throughout the treatment period, until 1 month after the last dose of study drug is administered.

All subjects who have AEs, whether considered associated with the use of the investigational product or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the AE result in death, a full pathologist's report should be supplied if and when available. **A plasma sample for PK should be collected, preferably within 24 to 48 hours of last intake of study drug, in any subject who develops an AE of hepatic injury or decompensation, or if early treatment discontinuation was due to an AE**. **The date and time of the PK draw and the last dose of study drug must be recorded in the eCRF.**

11.1.1.7. Pregnancy

If a female subject becomes pregnant during the study, the subject must be instructed to discontinue study drug and inform the investigator immediately. The investigator should report all pregnancies occurring in a subject or partner of a subject participating in the study that occur up to 3 months following the last dose of study drug to the CRO Drug Safety

within 24 hours of becoming aware of the pregnancy. The investigator should counsel the subject regarding the possible effects of prior study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE. Elective abortion procedures, without complications, should not be considered as AEs.

All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for this study. Furthermore, any SAE occurring as an adverse pregnancy outcome post-study must be reported to the CRO Drug Safety.

[redacted]

Pregnancies that occur more than 1 month after the subject has discontinued study drug do not require monitoring.

[redacted]

[redacted]

11.1.2. *Laboratory Assessments*

11.1.2.1. Measurement of Laboratory Assessments

A central laboratory will perform clinical safety laboratory tests. Urine pregnancy tests will be performed at the site using a dipstick method.

A complete list of all laboratory tests is provided in Appendix 20.5.

Refer to the Manual provided by Sponsor for details on the laboratories for this study.

Samples for hematology and serum chemistry will be prepared using standard procedures. Refer to the laboratory manual provided by Sponsor for further details and specifications for sample handling, processing, and shipment.

11.1.2.2. Clinically Significant Laboratory Abnormalities

Any laboratory test showing abnormal results (including those recorded as AEs) that are believed to be possibly/probably related to study drug treatment will be repeated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained. Whenever possible, the etiology of the abnormal findings will be documented on the eCRF. See Section 11.1.1.1.7 for a definition of clinically significant laboratory abnormalities.

11.1.3. *Toxicity Management*

Clinical events and clinically significant laboratory abnormalities will be graded according NCI CTCAE version 4.03 (Appendix 20.2).

11.1.3.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

11.1.3.2. Grade 3 Laboratory Abnormality or Clinical Event

For detailed management of subjects with ALT, AST, alkaline phosphatase (ALP), or bilirubin elevations, see Section 11.1.3.4.

For Grade 3 laboratory abnormalities**,** a confirmatory measurement should be obtained within 48 to 72 hours after the laboratory results become available.

[redacted]

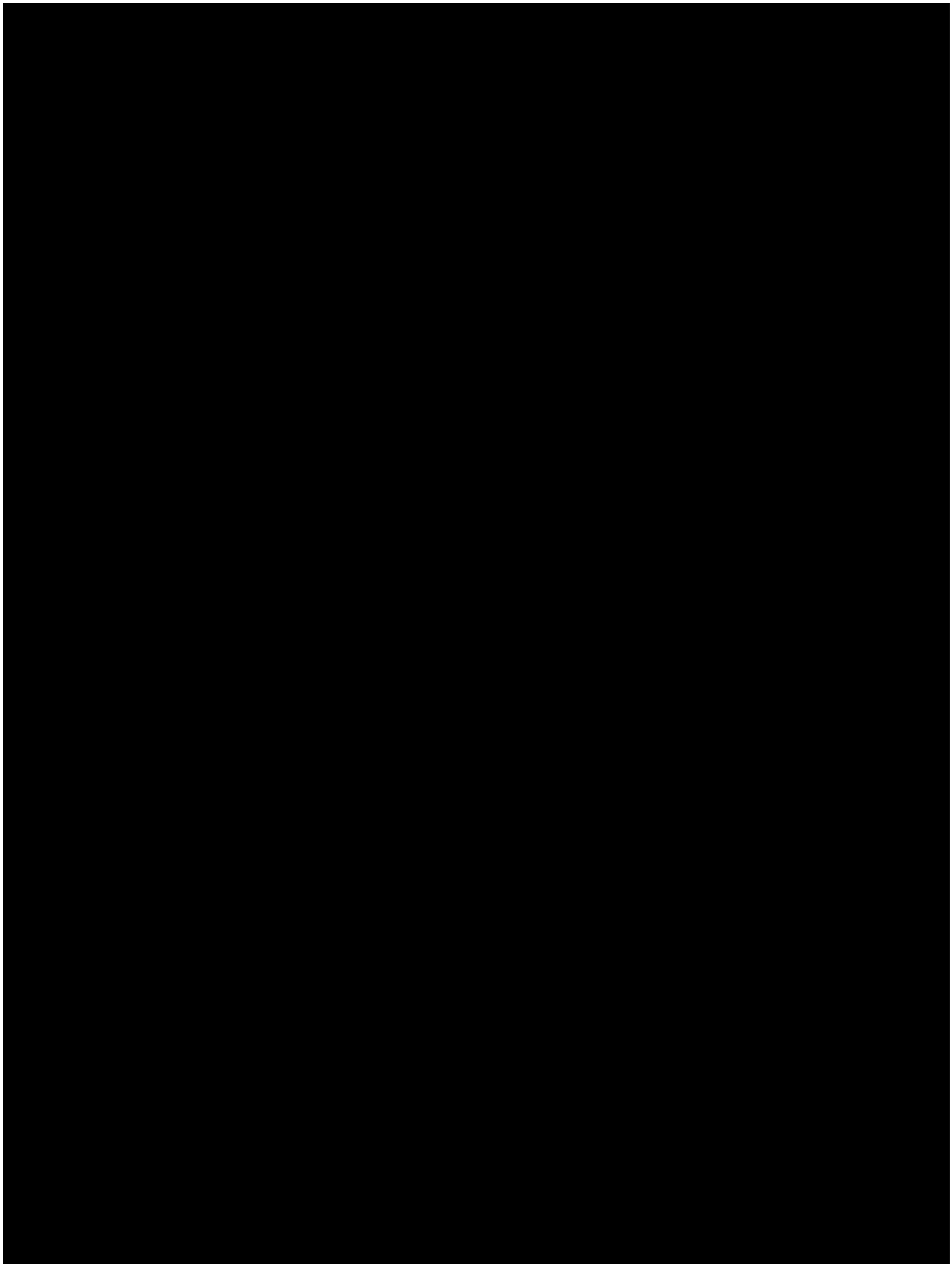
[redacted]

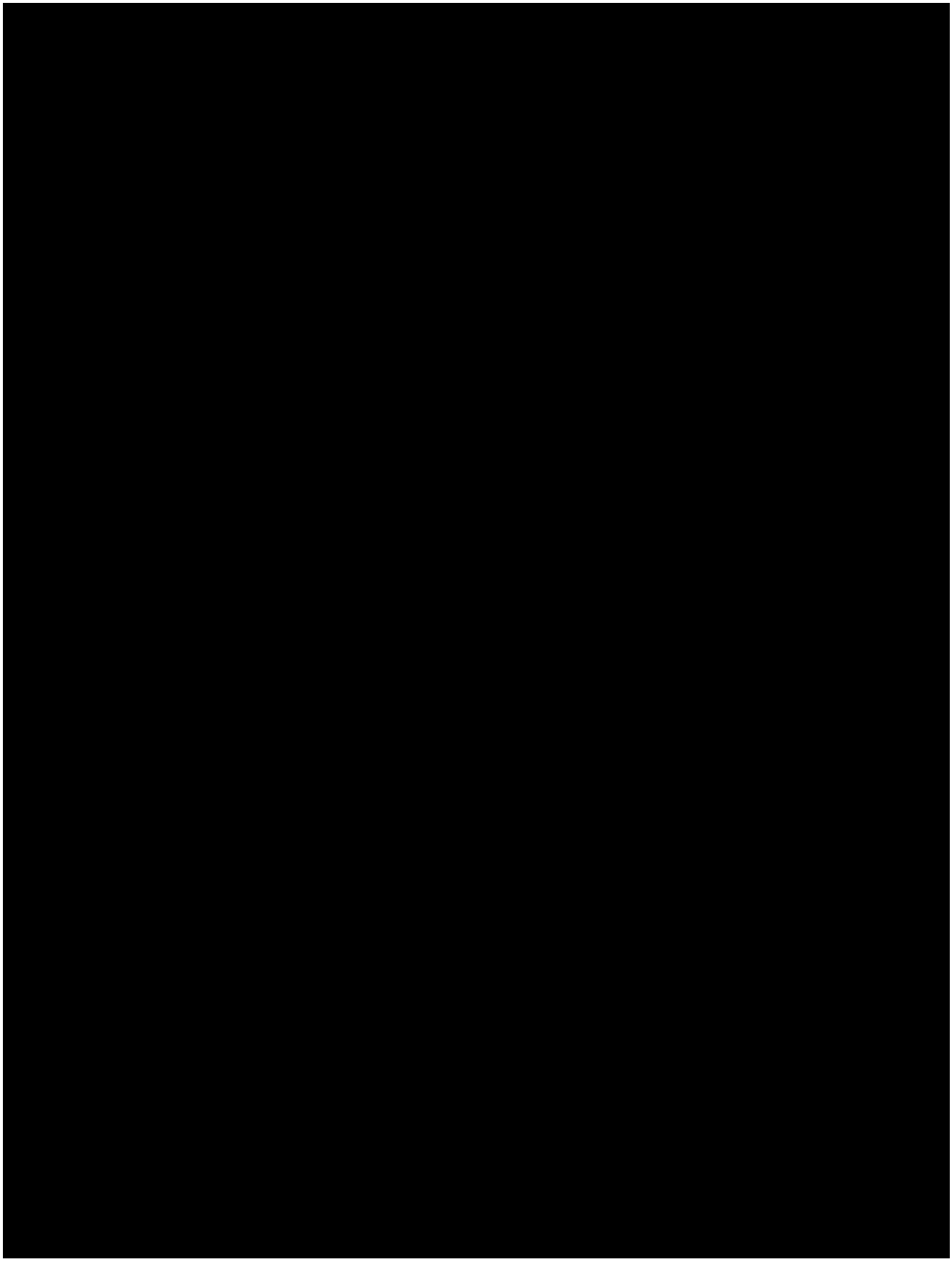
11.1.3.3. Grade 4 Laboratory Abnormality or Clinical Event

For detailed management of subjects with ALT, AST, ALP, or bilirubin elevations, see Section 11.1.3.4.

For Grade 4 laboratory abnormalities, a confirmatory measurement should be obtained within 48 to 72 hours after the laboratory results become available.

[redacted]





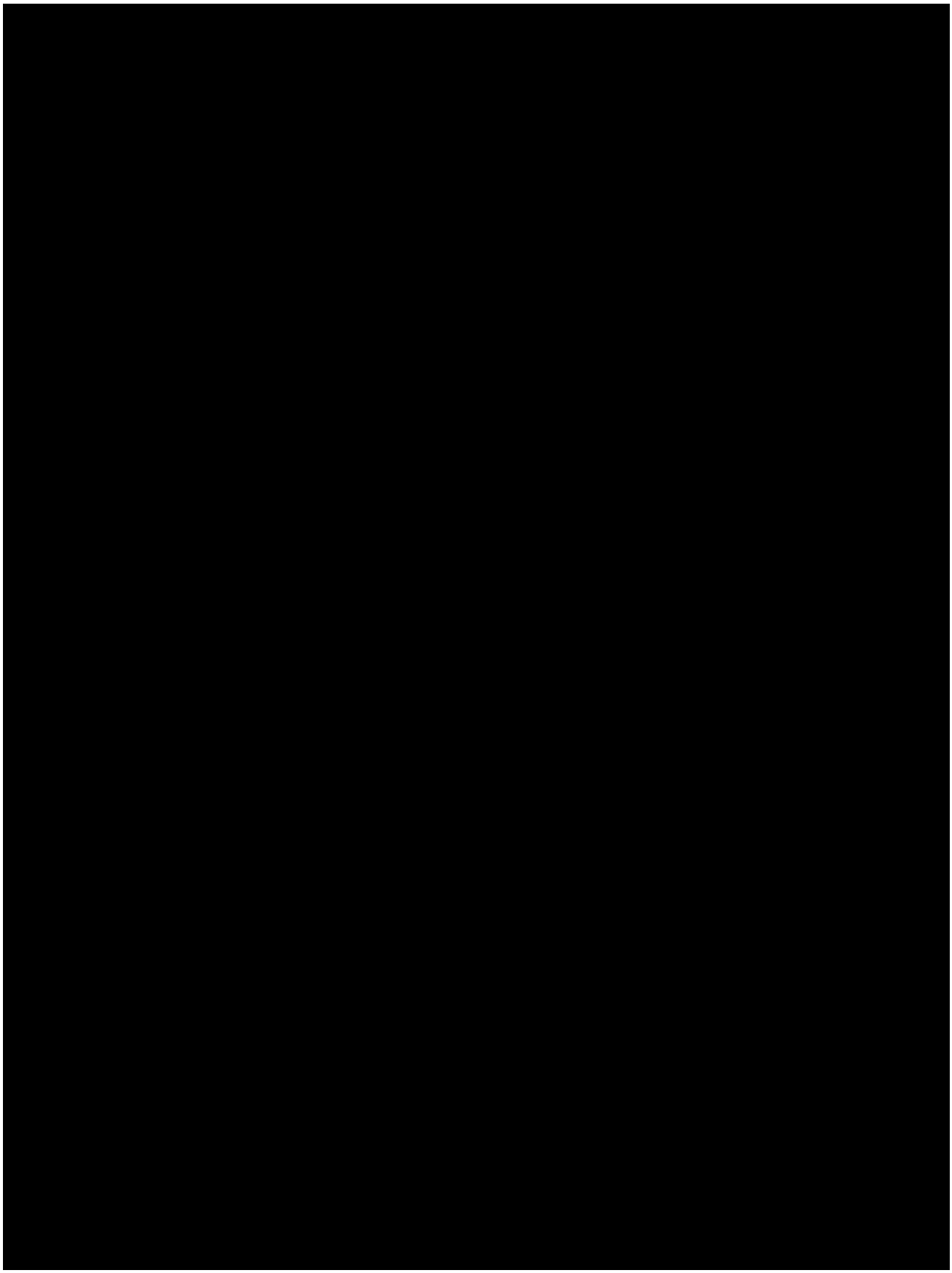
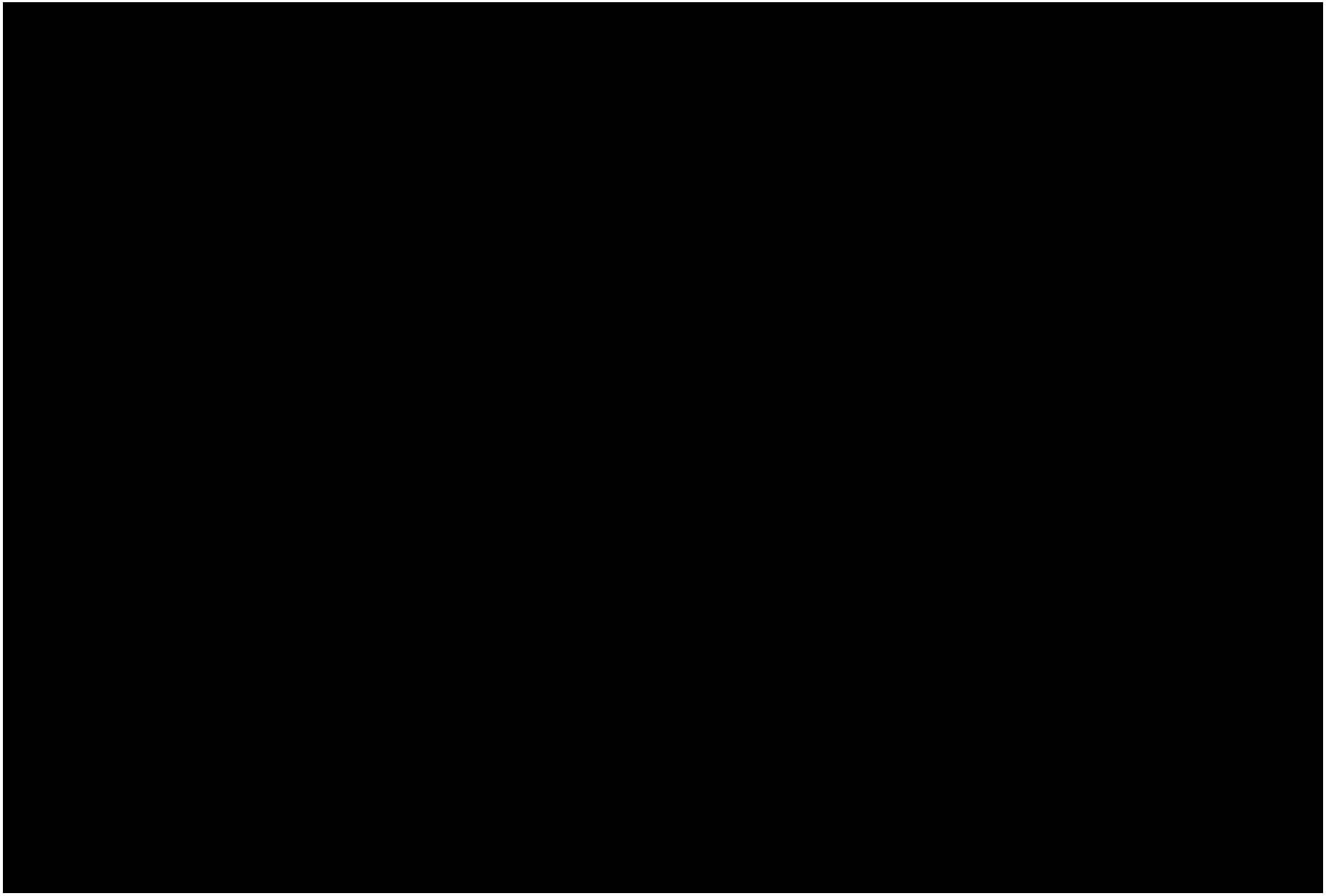
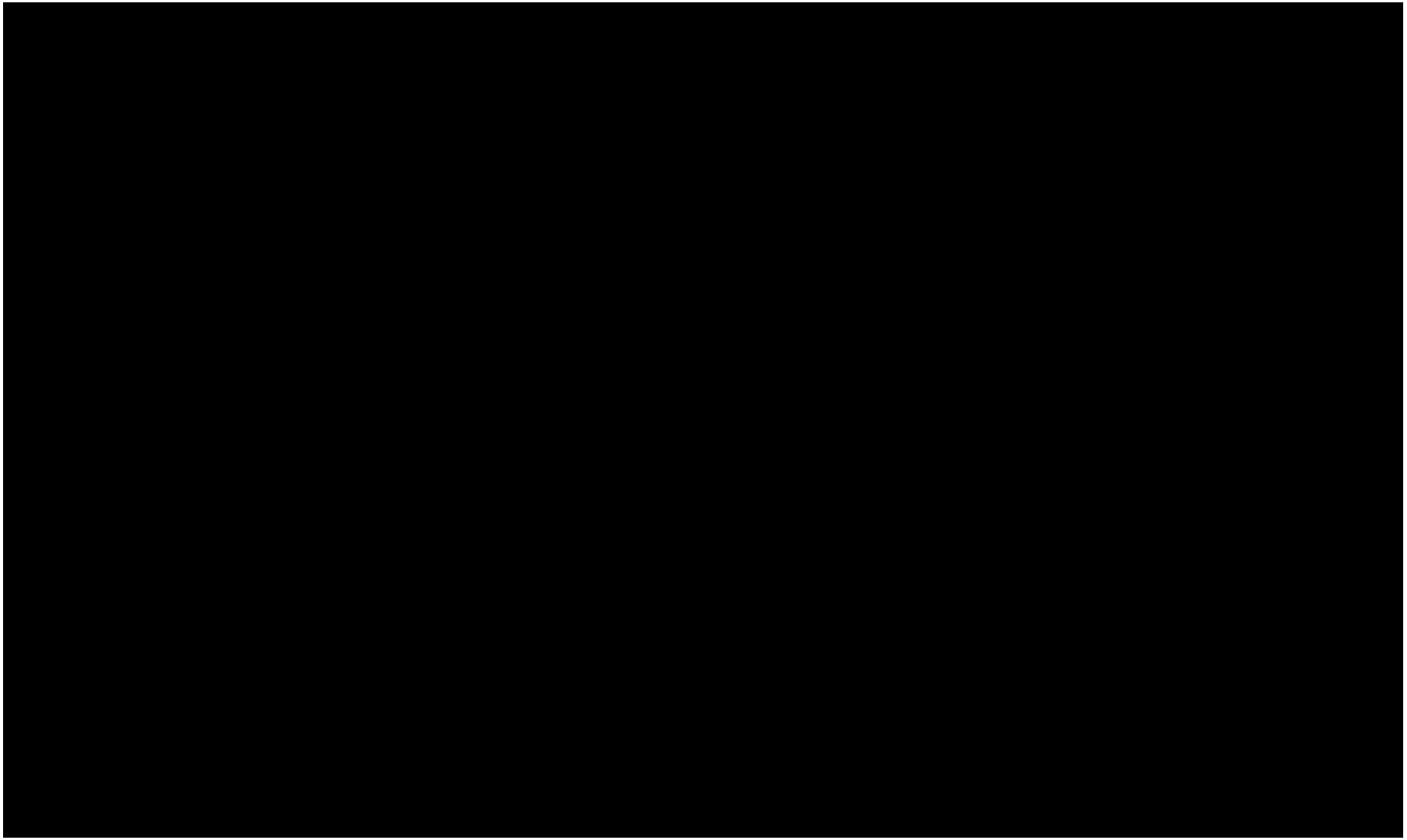


Table 11-1 Management of Subjects with Confirmed ALP, ALT, AST, or Bilirubin Elevations With or Without Liver-related Clinical Symptoms





11.2. Assessments of Drug Accountability and Medication Adherence

Drug accountability through the assessment of tablet counts will be performed by clinic staff at each clinic visit.

Subjects will be instructed to bring their bottles of study drug (used and unused) with them to every visit. The investigator, or designee, will count all returned study drug to determine compliance. Subjects will receive sufficient number of study drug bottles and be reminded that 1 tablet of study drug must be taken once daily with food.

If the study drug compliance drops below 80% at any given time during the Treatment Period, the investigator, or designee, should discuss compliance with subject and counsel the subject appropriately. Nonadherence includes missed doses in addition to taking the wrong dose. The investigator must encourage compliance with the study drug and with the study procedures at all times.

12. STATISTICS

No inferential statistical testing will be conducted for this continued access study. Summaries of demographics, baseline characteristics, treatment exposure, and safety parameters will be analyzed by descriptive statistics for the continuous variables and frequency counts with incidence rates for the dichotomous or categorical variables.

12.1 Safety

Duration of exposure (last day minus first day, plus 1) will be summarized. All AEs will be listed for individual subjects showing both verbatim and MedDRA preferred terms. AEs will be tabulated by the preferred term and system-organ classification. The occurrence of TEAEs will be summarized using MedDRA preferred terms and system organ classifications. Summaries will also be provided by severity, seriousness and relationship to study drug.

Descriptive summaries of clinical laboratory results will be presented. Laboratory abnormalities will be graded according to NCI CTCAE version 4.03 if recorded as an AE and categorized as a TEAE. The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized by severity grade. Laboratory toxicity shifts from baseline to post-baseline assessments will be summarized. Changes from baseline in laboratory tests will be summarized.

Prior and concomitant medications will be coded based on a World Health Organization preferred term and drug classification. The number and percent of subjects taking concomitant medications will be summarized using preferred terms and drug classifications.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Sponsor Audits

During the study, individuals from the Sponsor Quality Assurance department and/or their authorized representative may visit the investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the investigator's adherence to the protocol, applicable regulations, and Sponsor's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the investigator will be contacted by Sponsor to arrange a convenient time for this visit. The investigator and staff are expected to cooperate with the auditors and allow access to all subject records supporting the eCRFs and other study-related documents.

13.2. Inspection by Regulatory Authorities

At some point during the investigational product's development program, a regulatory authority may visit the investigator to conduct an inspection of the study and the site. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify Sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

14. ETHICS AND PROTECTION OF HUMAN SUBJECTS

14.1. Compliance Statement

The investigator agrees to conduct the study in compliance with the protocol, ICH GCP guidelines, and all local and national regulations.

The investigator must adhere to the protocol as described in this document and agree that deviations to the protocol, with the exception of medical emergencies, must be discussed and approved by Sponsor prior to seeking approval from the IRB/IEC. The investigator is responsible for enrolling subjects who have met the protocol inclusion and exclusion criteria or must have obtained prior documented approval from Sponsor prior to enrollment in the study. The IRB/IEC that granted original approval, or the IRB/IEC currently responsible for overseeing the conduct of the study, must be notified of all changes in and deviations from the protocol that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation. The investigator must send a copy of the approval letter from the IRB/IEC to Sponsor or CRO and retain the original in the site study regulatory file.

14.2. Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to assure that all aspects of the ethics review are conducted in accordance with the Declaration of Helsinki (October 2008) as described in the ICH E6: GCP, and/or local laws, whichever provides the greatest level of protection for the study participants. The protocol and any information supplied to the subject to obtain informed consent, including written ICF(s), subject recruitment procedures (eg, advertisements), and written information to be provided to subjects (information leaflets), must be reviewed and approved by a qualified IRB/IEC prior to enrollment of participants in the study. Prior to initiation of the study, Sponsor must receive documentation of the IRB/IEC approval, which specifically identifies the study/protocol, and a list of the committee members.

Amendments to the protocol and revisions to the informed consent must also be submitted to and, if required, approved by the IRB/IEC.

Investigators must submit progress reports to the IRB/IEC in accordance with the IRB/IEC requirements. Annual re-approval of the study must be obtained. Copies of progress reports and annual re-approvals must be sent to Sponsor.

When Sponsor provides the investigator with a safety report, the investigator must promptly forward a copy to the IRB/IEC.

After completion or termination of the study, the investigator must submit a final report to the IRB/IEC and to Sponsor.

The investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB/IEC.

The investigator is responsible for conducting the study in accordance with the protocol, all applicable laws, regulations, and GCP according to ICH guidelines.

14.3. Informed Consent

Preparation of the consent form is the responsibility of the investigator and Sponsor or designee and must include all elements required by the ICH, GCP, and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

A template will be provided by Sponsor or designee. Sponsor or designee must review and approve all changes to site-specific ICFs.

The consent form must include a statement that Sponsor or designee and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the investigator must have the IRB/IEC's written approval/favorable opinion of the written ICF and any other information to be provided to the subjects.

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them.

An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

A copy of the signed consent document must be given to the subject. The original signed consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The investigator must inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

14.4. Subject Confidentiality

Applicable data privacy laws and regulations must be adhered to. The investigator and Sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, Health Insurance Portability and Accountability Act [HIPAA]). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Subject names will not be supplied to Sponsor. Only the subject number and subject initials will be recorded in the eCRF, and if the subject name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

14.5. Study Conduct

The study will be conducted in compliance with the Declaration of Helsinki (October 2008) and the ICH E6 Guideline for GCP. All national, state, and local laws of the pertinent regulatory authorities will be followed.

If it is necessary to amend either the protocol or the ICF, the investigator will be responsible for ensuring that the IRB/IEC reviews and approves the amended documents. Amended ICFs must be obtained and used for obtaining consent from new subjects.

14.6. Study Discontinuation

Both the Sponsor and the investigator reserve the right to terminate the study, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination, and send a copy of the notification to Sponsor or CRO and retain one copy for the site study regulatory file.

15. DATA HANDLING AND RECORD KEEPING

15.1. Data Management Responsibilities

Laboratory data will be imported to the database electronically.

All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of Sponsor or its designee. The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures completed.

15.2. Data Handling and Record Keeping

15.2.1. *Data Collection and Retrieval*

The investigative site will be provided with eCRFs in which to record all the protocol-specified data for each subject in this study. Entries made in the eCRF must be verifiable against source documents, or in certain circumstances as directed by Sponsor, entries will have been directly entered into the eCRF; in such cases, the entry in the eCRF will be considered as the source data. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The investigator will be responsible for reviewing all data and eCRF entries and will sign and date the designated pages in each subject's eCRF, verifying that the information is true and correct.

Queries generated by Data Management at Sponsor will be sent to the study site for resolution. The investigator is responsible for the review and approval of all responses to eCRF queries.

15.2.2. *Records Retention*

The investigator must ensure that all records pertaining to the conduct of the clinical study, ICFs, drug accountability records, source documents, and other study documentation are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

The investigator must not destroy any records associated with the study without receiving approval from Sponsor. The investigator must notify Sponsor in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, Sponsor must be contacted to arrange alternative record storage options.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable provided it is legible and is a verified copy of the original document.

All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in

compliance with applicable record retention regulations. Sponsor will retain the original eCRF data and audit trail.

15.2.3. *Study Monitoring and Access to Source Documents*

Qualified representatives of Sponsor or its designees ("study monitors") may monitor the study according to a predetermined monitoring plan. Monitoring visits provide Sponsor with the opportunities to do the following:

- Evaluate the progress of the study
- Verify the accuracy and completeness of eCRFs
- Assure that all protocol requirements, applicable laws and/or regulations, and investigator's obligations are being fulfilled
- Resolve any inconsistencies in the study records

If a monitoring visit is scheduled, the investigator must allow the study monitors to review, at mutually convenient times during the study and after the study has been completed, all eCRFs and office, hospital, and laboratory records supporting the participation of each subject in the study. The eCRFs and other documentation supporting the study must be kept up-to-date by the investigator and the research staff at the investigative site. These study materials must be available for review by the study monitor, and/or other qualified representatives of Sponsor, at each monitoring visit.

The study monitor will review the various records of the study (eCRFs, subject medical and laboratory records, and other pertinent data). The study monitor will verify the eCRF data against original source documentation for accuracy and completeness. The study monitor will identify data discrepancies and collaborate with the investigator and research staff to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded on a "Protocol Deviation Log." The study monitor will follow an "Issue Escalation" plan in order to ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

16. PUBLICATION POLICY

Neither the Institute nor the Principal Investigator shall have the right to publish or present any materials made available or generated through the Study except as specified herein.

The Institute and the Principal Investigator shall be free to publish or present site-specific results of the Project subject to the following conditions:

a. In the case of a Study conducted at multiple institutions or study sites, Institute and Principal Investigator agree that they will not submit a publication or make any presentation prior to the initial publication of the joint, multi-center results of the Study, which shall be coordinated by Sponsor;

b. Institute and Principal Investigator agree that any authorized publication or presentation shall not reveal any of the Sponsor's Information without the expressed written consent of the Sponsor;

c. Institute and Principal Investigator shall send Sponsor a copy of any such proposed publication for Sponsor's review and comment ninety (90) days prior to submission for publication and shall not disclose to any third party prior to such submission any data, results, discoveries, or inventions arising from the clinical research study regardless of a determination of the ownership of rights to such material;

d. Institute and Principal Investigator, upon Sponsor's request, shall delete any of Sponsor's Information in the proposed publications; and shall not include raw data in such publications, except in the case of any information or data to the extent necessary to present the analysis in a manner consistent with generally accepted scientific and academic standards; and

e. Institute and Principal Investigator, upon Sponsor's request, shall delay submission for any publication or presentation while the Sponsor files applications for patents or other registrations of intellectual property rights.

Any publication or presentation, including summaries or abstracts will appropriately reference the support received from the Sponsor for the conduct of the Project The parties agree that any authorized publication or presentation shall comply with applicable guidelines set forth by International Committee of Medical Journal Editors (ICMJE) and Good Publications Practice for Communicating Company Sponsored Medical Research (GPP2). Institute agrees that pursuant to any authorized publication or presentation, authors must disclose in their manuscripts, journal submissions, and elsewhere as appropriate or required, any potential conflicts of interest, including their financial or personal relationship with Sponsor, and the names of any individuals who have provided editorial support for any manuscript or other publication.

Sponsor shall have the right to identify Institute as the site at which the Study was conducted and to identify those individuals responsible for conducting the Study, including Principal Investigator, and to provide any other information as necessary to post the Study on

www.clinicaltrials.gov or any other applicable public registries as required by applicable laws and regulations.

17. REFERENCES

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18. SPONSOR'S SIGNATURE PAGE

Open-label Rollover Study of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects with Nonalcoholic Steatohepatitis (NASH)

Protocol Issue Date: 01 December 2016

Global Amendment 1 Issue Date 14 Apr 2018

I have reviewed and approved the attached version, cited above, of Protocol 3152-201-002.

[redacted]

Date

Senior Vice President, Liver Therapeutic Area Head, Allergan plc

19. INVESTIGATOR'S SIGNATURE PAGE

Open-label Rollover Study of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects with Nonalcoholic Steatohepatitis (NASH)

Protocol Issue Date: 01 December 2016

Global Amendment 1 Issue Date 14 Apr 2018

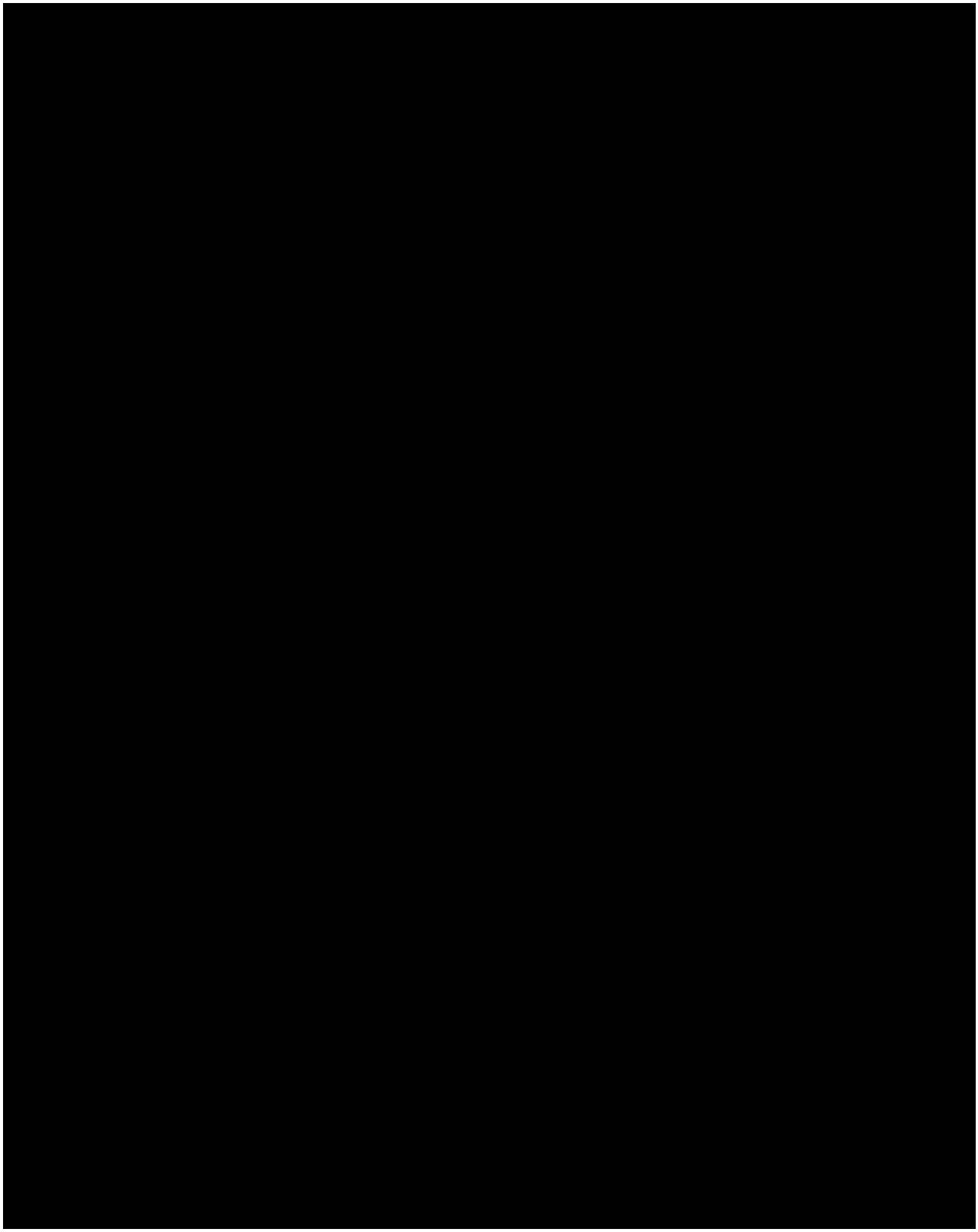
I have read, understand, and agree to follow the attached version, cited above, of Protocol 3152-201-002.

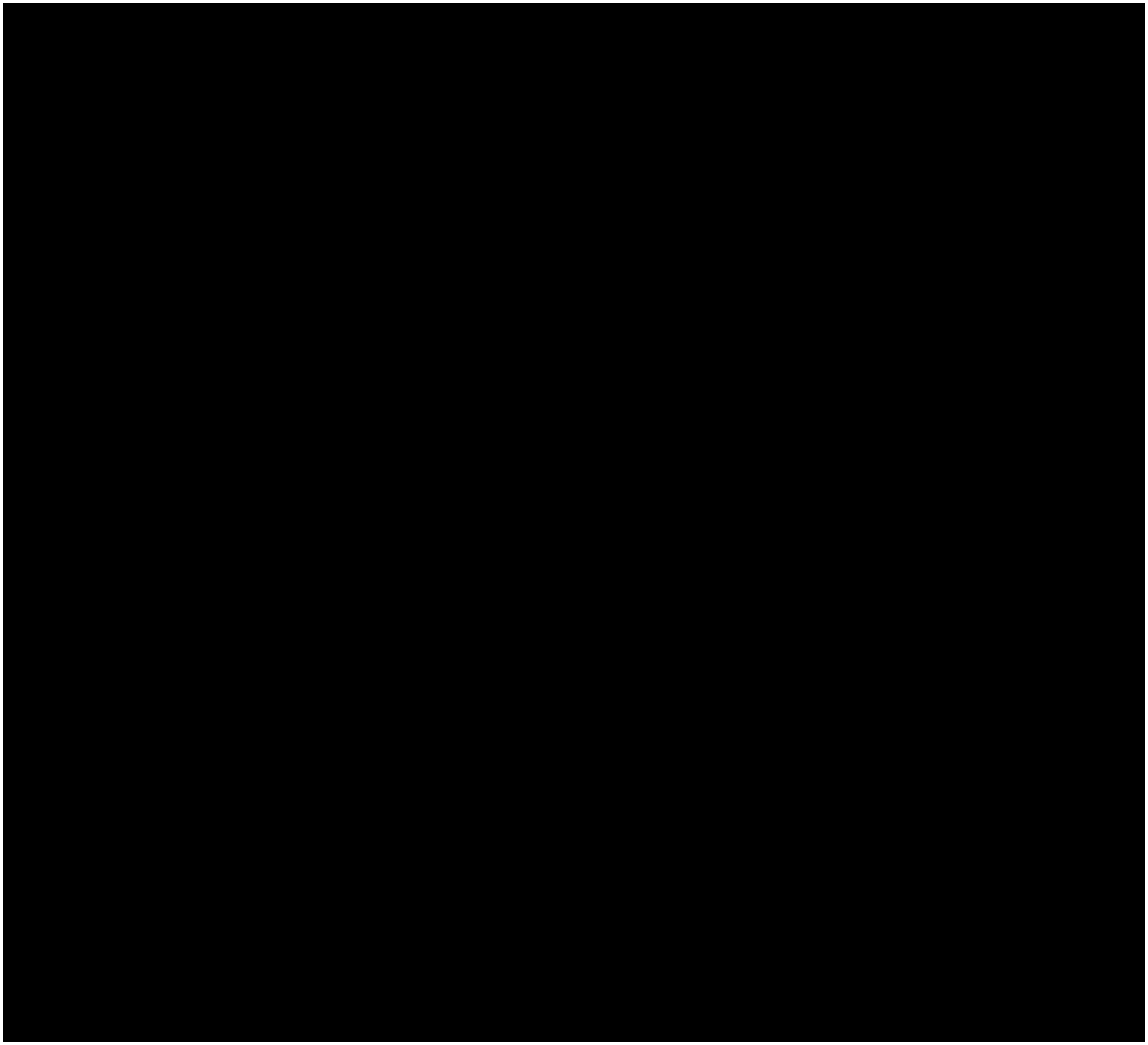
Principal Investigator Name (Print)	Signature
Date	Site Number

20. APPENDICES

20.1. Schedule of Assessments

Table 20-1 Schedule of Assessments





20.2. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Quick Reference

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) is a descriptive terminology which can be utilized for adverse event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

System Organ Class

System Organ Class (SOC), the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (eg, SOC investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (grade).

CTCAE Terms

An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA lowest level term (LLT).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A semi-colon indicates ‘or’ within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5 options for grade selection.

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

20.3. Information on Contraception Effectiveness

Trussell J. Contraceptive failure in the United States. Contraception 2004;70:89-96.

20.4. Disallowed Medications

Caution should always be exercised when administering concomitant medications based on the individual medication profile and clinical risk-benefit assessment.

The subject must not take the following disallowed medications at any time during the study, from Screening through the 1-Month Follow-up Visit.

Disallowed Medications				
Medicinal Product Class	**CYP3A4 Substrates with Narrow Therapeutic Index**	**Strong/moderate CYP 3A4 Inducers**	**Strong CYP3A4 Inhibitors**	**Strong CYP2C8 Inhibitors**
Antibacterials		rifampin, nafcillin	clarithromycin, erythromycin, telithromycin	
Anticonvulsants		carbamazepine, phenytoin		
Antidepressants			nefazodone	
Antifungals			voriconazole, itraconazole, ketoconazole, posaconazole	
Antihistamines	astemizole			
Antipsychotics	pimozide			
Ergot Alkaloids	dihydroergotamine, ergonovine, ergotamine, methylergonovine			
Immunosuppressants			cyclosporine, tacrolimus	
Lipid-lowering Agents				gemfibrozil
Opioids	fentanyl, alfentanil IV alfentanil or fentanyl are not allowed for biopsies performed during the open label study or for any procedures requiring these medications after intake of study drug.			
Sedative/hypnotics	midazolam, triazolam **Exception**: Midazolam use is allowed for sedation for surgical procedures; however, for any procedures after intake of study drug, the first dose should be			

	decreased by 50% of the recommended dose and titrated according to the desired clinical response.			
Other	cisapride			

Disallowed Medications— BCRP Substrates	
Medicinal Product Class	**BCRP substrates**
Anti-inflammatory drugs	sulfasalazine
Antimetabolite drugs	methotrexate

Disallowed Investigational NASH Products	
Other	Eg, obeticholic acid, elafibranor, selonsertib

Disallowed Medications - Antivirals	
Medicinal Product Class	
Antivirals	All antivirals for the treatment of HIV, HBV, and HCV

The following medications, if used, should be used with caution as CVC (mild CYP3A4 inhibitor and BCRP inhibitor) may increase exposure of these CYP3A4 and BCRP substrates or these medications may affect the absorption of CVC. If used, these medications should be used at the lowest possible dose and for the shortest duration possible considering individual subject risk-benefit considerations. Clinical monitoring and dose titration are recommended to achieve the desired clinical response. Other medications of a similar class should be considered if possible. Consult the individual medication prescribing information for additional guidance.

Medicinal Product Class	**Drugs that are Allowed but Must be Taken with Precaution During Intake of Study Drug (Mechanism)**
Acid-reducing agents (H2 receptor antagonists, antacids, proton-pump inhibitors [PPIs])	Acid-reducing agents should be administered at least 2 hours after the CVC dose to ensure that adequate CVC concentrations are maintained. When possible, use of an H2 receptor antagonist (except cimetidine) or antacids is preferred over a proton pump inhibitor (PPI). It is recommended to start with the lowest dose of these agents and titrate according to clinical response. H2 receptor antagonists (eg, famotidine or ranitidine) should preferably be given from 2 to 12 hours after administration of study drug at a dose that does not exceed doses comparable to famotidine 40 mg daily. Antacids (eg, aluminum hydroxide, calcium carbonate, magnesium carbonate, magnesium hydroxide, or bismuth subsalicylate) should preferably be given at least 4 hours after administration of study drug due to their immediate effect in increasing gastric pH. PPIs (eg, omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, or dexlansoprazole) should preferably be given approximately 3 hours after administration of study drug at a dose that does not exceed doses comparable to omeprazole 20 mg daily. Due to the prolonged acid-reducing effect of PPIs (~16 – 24 hours), it is advised to follow these dosing recommendations to reduce their potential impact on CVC absorption at subsequent dosing.
Lipid-lowering agents	atorvastatin, simvastatin, lovastatin, (CYP3A4 substrates); pravastatin (CYP3A4 substrate, weak CYP2C8 inhibitor); rosuvastatin (BCRP substrate) The maximum recommended daily doses are as follows: atorvastatin 40 mg, simvastatin 20 mg, lovastatin 40 mg, pravastatin 40 mg, and rosuvastatin 20 mg; pitavastatin use is allowed without dose restriction. The medical monitor must be consulted prior to use of higher doses of statins than those recommended above.
PDE5 enzyme inhibitors	sildenafil, tadalafil, vardenafil (CYP3A4 substrates) The recommended starting doses for these medications are as follows: sildenafil 25 mg, tadalafil 2.5 mg, vardenafil 2.5 mg.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/uc m093664.htm

20.5. Clinical Laboratory Tests