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**Study ID: 652-205**

**Title:** PERSEUS: A Phase 2 Proof of Concept Study Investigating the Preliminary Efficacy and Safety of Cenicriviroc in Adult Subjects with Primary Sclerosing Cholangitis (PSC)

**Protocol Amendment 3 Date:** 14 June 2016



**Title:** **PERSEUS: A Phase 2 Proof of Concept Study Investigating the Preliminary Efficacy and Safety of Cenicriviroc in Adult Subjects with Primary Sclerosing Cholangitis (PSC)**

**Protocol Number:** **652-205**

**Product:** **Cenicriviroc Mesylate (CVC)**

**Phase of Study:** **Phase 2**

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### 3.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
[REDACTED]	[REDACTED]
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
[REDACTED]	[REDACTED]
ADR	adverse drug reaction
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
CRF	case report form
C <sub>max</sub>	maximum plasma concentration
[REDACTED]	[REDACTED]
CRA	clinical research associate
CVC	cenicriviroc
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
ECG	electrocardiogram
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
FDA	Food and Drug Administration
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
GCP	Good Clinical Practice
[REDACTED]	[REDACTED]
GPP	Good Publication Practice
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

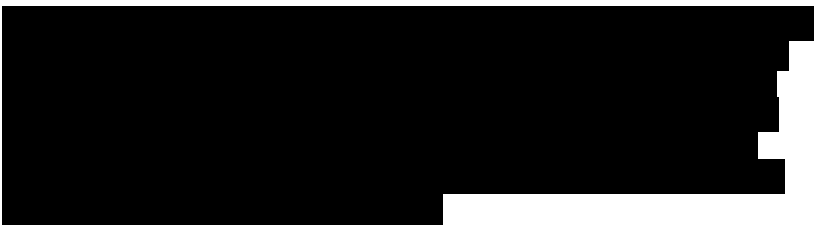


<b>Abbreviation</b>	<b>Definition</b>
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
IBD	inflammatory bowel disease
[REDACTED]	[REDACTED]
ICF	informed consent form
ICH	International Conference on Harmonisation
[REDACTED]	[REDACTED]y
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intention to treat
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
MedDRA	Medical Dictionary for Regulatory Activities
[REDACTED]	[REDACTED]
MRCP	magnetic resonance cholangiopancreatography
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
PK	pharmacokinetic(s)
PoC	proof of concept
PP	per protocol

<b>Abbreviation</b>	<b>Definition</b>
█	█
PSC	primary sclerosing cholangitis
QD	once daily (quaque die)
█	█
REB	Research Ethics Board
█	█
SAE	serious adverse event
█	█
█	█
SOC	System Organ Class
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
T <sub>1/2</sub>	half-life
TE	transient elastography
TEAE	treatment-emergent adverse event
█	█
Tobira	Tobira Therapeutics, Inc.
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
US	United States
UV	Ultraviolet

#### 4.0 SYNOPSIS

Title	PERSEUS: A Phase 2 Proof of Concept Study Investigating the Preliminary Efficacy and Safety of Cenicriviroc in Adult Subjects with Primary Sclerosing Cholangitis (PSC)
Clinical Phase	2
Indication	Treatment of PSC
Objective(s)	<p>Primary Objective:</p> <ul style="list-style-type: none"> <li>Evaluate effects of cenicriviroc (CVC) on serum alkaline phosphatase (ALP) over 24 weeks of treatment in adult subjects with PSC</li> </ul> <p>Secondary Objectives:</p> <ul style="list-style-type: none"> <li>To evaluate the safety and tolerability of CVC over 24 weeks in adult subjects with PSC</li> </ul>
Study Design	<p>This is a single-arm, open label, proof of concept (PoC) study of CVC in adult subjects with PSC. The main objective of this PoC study is to assess changes in ALP both individually and as a group, over 24 weeks of treatment with CVC.</p> <p>An informed consent form (ICF) will be signed prior to any screening activities. Screening will occur within 6 weeks before the Baseline Visit (Day 1). At the Screening visit, subjects will undergo all eligibility evaluations per the schedule of assessments. Subjects who meet all the eligibility criteria will be scheduled for a Baseline visit (Day 1) and enrolled in the study. The first dose of CVC will be given on-site at the Baseline visit. Subjects will return to the study site for on-treatment evaluations at Weeks 4, 8, 12, 16 and 24. Approximately 4 weeks after the last dose of study drug (Week 28), subjects will undergo follow-up evaluations. Subjects who discontinue study drug prior to completion of 24 weeks of treatment will be required to return to the clinic for an Early Discontinuation Visit.</p>
Treatment Duration	24 weeks
Number of Subjects	Approximately 25 subjects in total, all of whom will be treated with open label CVC. If a subject discontinues from the study for any reason other than safety, a replacement subject will be considered.
Number of Study Centers	Approximately 10 centers in Canada and the United States
Target Population	Adult subjects with clinically diagnosed PSC
Inclusion Criteria	<ol style="list-style-type: none"> <li>Adult male and female subjects aged 18-75 years with chronic cholestatic liver disease for at least 6 months</li> <li>Clinical diagnosis of PSC as evident by chronic cholestasis of more than six months duration with either a consistent magnetic resonance cholangiopancreatography (MRCP)/endoscopic retrograde cholangiopancreatography (ERCP) showing sclerosing cholangitis, or a liver biopsy taken at any time consistent with PSC in the absence of a documented alternative etiology for sclerosing cholangitis. If diagnosis of PSC was made by histology alone, it must require the presence of fibro-obliterative lesions (i.e., onion skin lesions).</li> <li>Subjects with or without Inflammatory Bowel Disease (IBD) are allowed. If subject has IBD, documented evidence of IBD either by prior endoscopy or in previous medical records, for <math>\geq 6</math> months. In addition, subjects will be required to enter the study with a Partial Mayo Risk score of 0-3, inclusively</li> </ol>

	<ol style="list-style-type: none"> <li>4. In subjects receiving treatment with ursodeoxycholic acid (UDCA), therapy must be stable for at least 3 months, and at a dose not greater than 20 mg/kg/day</li> <li>5. Serum ALP <math>\geq 1.5 \times</math> upper limit of normal (ULN)</li> <li>6. </li> <li>7. Ability to understand and sign a written informed consent form (ICF)</li> <li>8. Subjects receiving allowed concomitant medications need to be on stable therapy for 28 days prior to the Baseline Visit (see <a href="#">Section 9.3</a> for list of restricted medications), with the exception of UDCA in which subjects need to be on stable therapy for <math>\geq 3</math> months</li> </ol>
<p>Exclusion Criteria</p>	<ol style="list-style-type: none"> <li>1. Presence of documented secondary sclerosing cholangitis (such as ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis) on prior clinical investigations</li> <li>2. Small duct PSC</li> <li>3. Presence of percutaneous drain or bile duct stent</li> <li>4. History of cholangiocarcinoma or high clinical suspicion over dominant stricture within 1 year by MRCP/ERCP or clinical judgement</li> <li>5. Ascending cholangitis within 60 days prior to Screening</li> <li>6. Alcohol consumption greater than 21 units/week for males or 14 units/week for females (one unit of alcohol is <math>\frac{1}{2}</math> pint of beer [285 mL], 1 glass of spirits [25 mL] or 1 glass of wine [125 mL])</li> <li>7. Prior or planned liver transplantation</li> <li>8. Presence of alternative causes of chronic liver disease, including alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cirrhosis, autoimmune hepatitis</li> <li>9. History of cirrhosis and/or hepatic impairment (Child-Pugh classes A, B and C) and/or hepatic decompensation including ascites, encephalopathy or variceal bleeding. Subjects who show evidence of significant worsening of hepatic function will be excluded</li> <li>10. Subjects with evidence of cirrhosis, as determined by local transient elastography (TE; e.g., FibroScan<sup>®</sup>) values of <math>\geq 13.0</math> kPa, taken within the last 6 months. If TE has not been conducted within the 6 months prior to screening then one will be conducted during the screening period and can be used as the Baseline value</li> <li>11. Moderate to Severe active IBD or flare in colitis activity within the last 90 days requiring intensification of therapy beyond Baseline treatment. Subjects with stable mild to moderate IBD, who are on treatment, are allowed provided they are stable for 3 months with 5-amino salicylic acid drugs or Azathioprine (allowed dose of azathioprine is 50-200 mg/day)</li> <li>12. Use of oral prednisolone <math>&gt; 10</math> mg/day, biologics and/or hospitalization for colitis within 90 days are disallowed</li> </ol>

	<p>13. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT); above the allowed cut-offs, as determined by the Screening values:</p> <ul style="list-style-type: none"> <li>• AST &gt; 200 IU/L males and females</li> <li>• ALT: males &gt; 250 IU/L and females &gt; 200 IU/L</li> </ul> <p>14. Total Bilirubin and Direct Bilirubin; above the allowed cut-offs, as determined by the Screening values:</p> <ul style="list-style-type: none"> <li>• Total Bilirubin &gt; 2.0 mg/dL</li> <li>• Direct Bilirubin &gt; 0.8 mg/dL</li> </ul> <p>15. International normalized ratio (INR) &gt; 1.3 in the absence of anticoagulants.</p> <p>16. Immunoglobulin G4 (IgG4) &gt; 4 × ULN at Screening or evidence of IgG4-related sclerosing cholangitis</p> <p>[Redacted text block consisting of approximately 20 lines of blacked-out content]</p> <p>34. Any other clinically significant disorders or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with the dosing and protocol requirements</p>
Test Article(s)	CVC 150 mg tablet
Dosage and Administration	CVC 150 mg, administered orally once daily and taken every morning with food
Placebo	There is no placebo group in this study
Study Procedures/ Frequency	Screening will occur within 6 weeks before the Baseline Visit (Day 1). Eligible subjects will be seen at Baseline (Day 1), Week 4, Week 8, Week 12, Week 16, and Week 24. A safety follow-up visit will be conducted at Week 28 ± 3 days

	<p>(i.e., 4 weeks after last intake of study medication) or at the time of early termination (if applicable). On visit days, subjects will be need to come into the clinic fasting. Blood samples will be collected prior to dosing. Subjects will be required to bring in study medication on the days of clinic visits and dosing will be conducted on site with a morning snack.</p> <p>Study procedures include:</p> <ul style="list-style-type: none"> <li>• The informed consent will be reviewed and signed at the Screening 1 visit, as well as all eligibility assessments, per the schedule of evaluations</li> <li>• IgG Total, IgG1 and IgG4 will be collected at Baseline, and Week 24 (IgG4 will also be collected at Screening)</li> <li>• Clinical laboratory tests will be measured at Screening, Baseline and each study visit: clinical chemistries, hematology, liver parameters including ALP, bilirubin, serum albumin, serum bile acids, gamma-glutamyl transferase (GGT), ALT and AST</li> <li>• Partial Mayo Risk scoring for assessment of IBD will be conducted at Baseline and at each visit</li> <li>• Transient elastography will be assessed once during the Screening period (between Screening to Baseline) and at Week 24</li> <li>• [REDACTED]</li> <li>• [REDACTED]</li> <li>• [REDACTED]</li> <li>• Serum samples will be collected and stored for future analysis for biomarkers of interest at Baseline, Weeks 12 and 24</li> <li>• Plasma pharmacokinetic (PK) samples will be drawn pre-dose and post-dose at Baseline and at Weeks 12, and 24</li> <li>• Weight will be measured at Screening, Baseline and Weeks 12 and 24; height will be measured only at Screening</li> <li>• Complete or symptom directed physical examinations and laboratory analyses will be performed at each visit</li> <li>• Electrocardiograms will be performed at Baseline and at Weeks 12 and 24</li> <li>• Adverse events and concomitant medications will be assessed at each visit</li> </ul>
<p>Efficacy Evaluation</p>	<p>The primary endpoint for this study is the percent change from Baseline through Week 24 in serum alkaline phosphatase</p> <p>[REDACTED]</p> <ul style="list-style-type: none"> <li>• [REDACTED]</li> <li>• [REDACTED]</li> <li>• [REDACTED]</li> </ul>
<p>Safety Evaluation</p>	<p>Safety endpoints:</p> <ul style="list-style-type: none"> <li>• Evaluate the safety and tolerability of CVC through 24 weeks of treatment in adult subjects with PSC</li> <li>• Evaluate the proportion of subjects with a treatment-emergent AE or a clinically significant laboratory abnormality (overall and of any given type)</li> </ul>

	<ul style="list-style-type: none"> <li>• Evaluate the proportion of subjects who discontinue due to an AE</li> </ul>
Other Exploratory Evaluation	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
Statistical Analysis	<p>This is a single arm open label study in adult subjects with PSC. Descriptive statistical methods will be used to summarize data from this study. Displays of treatment-related efficacy and safety profiles for each patient and overall will be summarized.</p>
Efficacy Analysis	<p>Percent changes in ALP from Baseline will be summarized using descriptive statistics for the respective pre-treatment and on-treatment visits. A repeated measures mixed model will be fit to the data for all pre-treatment and on-treatment visits, and this model will include explanatory variables for visits and Baseline; and it will have compound symmetry as the covariance structure. Through this model, 95% confidence intervals will be produced for the mean percent change at each visit. Also, a comparison of pre-treatment change per week with on-treatment change per week will be made through an estimate specification and the corresponding 95% confidence interval. Descriptive comparisons will be made with historical data where UDCA was administered and/or with the natural history of the disease, as appropriate.</p>
Safety Analysis	<p>Clinical laboratory and safety data will be summarized using descriptive analysis.</p>
Sample Size	<p>Each patient will serve as their own control when observing ALP relative to Baseline. [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>

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## 6.0 STUDY OBJECTIVES, ENDPOINTS AND EVALUATIONS

### Study Objectives:

- Evaluate effects of CVC on serum ALP over 24 weeks of treatment in adult subjects with PSC
- To evaluate the safety and tolerability of CVC over 24 weeks in adult subjects with PSC

### Primary Endpoint:

- The primary endpoint for this study is the percent change from Baseline through Week 24 in serum alkaline phosphatase

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

### Safety Evaluations:

- Evaluate the safety and tolerability of CVC through 24 weeks of treatment in adult subjects with PSC
- Evaluate the proportion of subjects with a treatment-emergent AE or a clinically significant laboratory abnormality (overall and of any given type)
- Evaluate the proportion of subjects who discontinue due to an AE

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

## 7.0 INVESTIGATIONAL PLAN

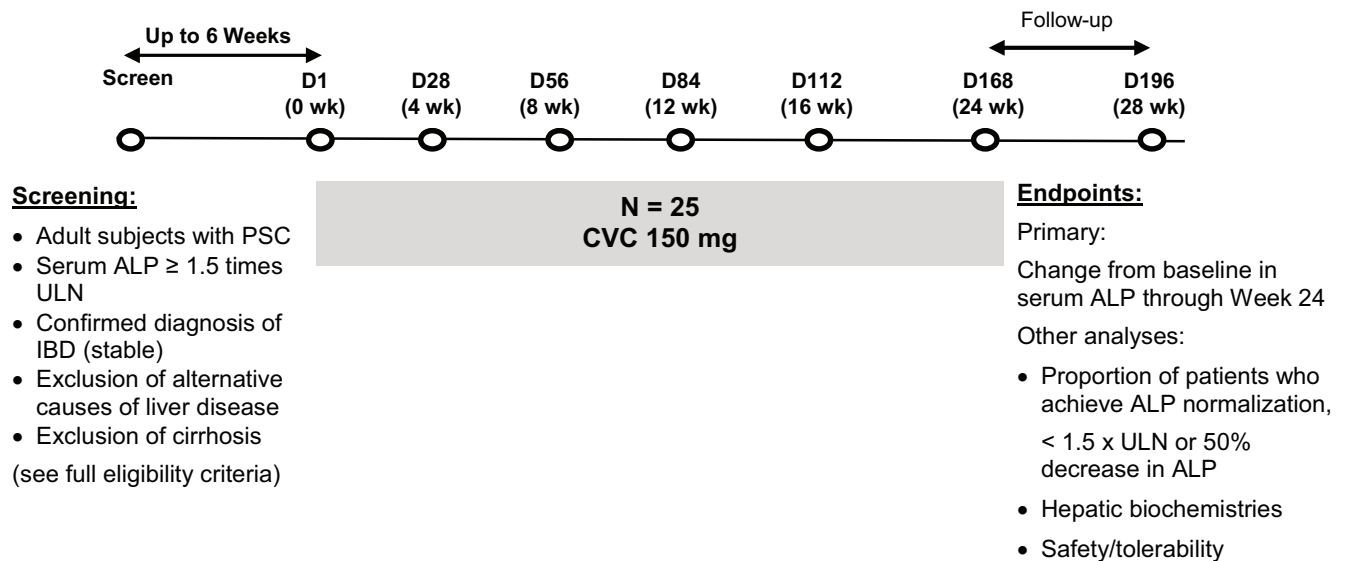
### 7.1 Overall Study Design and Plan

This is a Phase 2, single-arm, open label, proof of concept study of CVC in approximately 25 adult subjects with PSC. [REDACTED]

Screening will occur within 6 weeks before the Baseline Visit. Subjects will review the ICF and provide written consent before any screening procedures taking place. After completing Screening visit, eligible subjects can be scheduled for study enrollment. At the Baseline Visit, subjects who have met all the eligibility criteria will be enrolled in the study and begin treatment with CVC. Subjects will return to the study site for on-treatment evaluations at Weeks 4, 8, 12, 16 and 24. Approximately 4 weeks after the last dose of study drug (Week 28), subjects will undergo follow-up evaluations. Subjects who discontinue study drug prior to completion of 24 weeks of treatment will be required to return to the clinic for an Early Discontinuation Visit.

The study design is illustrated in [Figure 7-1](#).

**Figure 7-1 Study Design Schematic**



## 8.0 STUDY POPULATION


### 8.1 Number of Subjects

Approximately 25 subjects are planned for enrollment. Eligible adult patients with PSC will be treated for 24 weeks with CVC.

### 8.2 Inclusion Criteria

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

1. Adult male and female subjects aged 18-75 years with chronic cholestatic liver disease for at least 6 months
2. Clinical diagnosis of PSC as evident by chronic cholestasis of more than six months duration with either a consistent magnetic resonance cholangiopancreatography (MRCP) /endoscopic retrograde cholangiopancreatography (ERCP) showing sclerosing cholangitis, or a liver biopsy taken at any time consistent with PSC in the absence of a documented alternative etiology for sclerosing cholangitis. If diagnosis of PSC was made by histology alone, it must require the presence of fibro-obliterative lesions (i.e., onion skin lesions)
3. Subjects with or without Inflammatory Bowel Disease (IBD) are allowed. If subject has IBD, documented evidence of IBD either by prior endoscopy or in previous medical records, for  $\geq 6$  months. In addition, subjects will be required to enter the study with a Partial Mayo Risk score of 0-3, inclusively
4. In subjects receiving treatment with UDCA, therapy must be stable for at least 3 months, and at a dose not greater than 20 mg/kg/day
5. Serum ALP  $\geq 1.5 \times$  ULN.

- 
7. Ability to understand and sign a written informed consent form (ICF)
  8. Subjects receiving allowed concomitant medications need to be on stable therapy for 28 days prior to the Baseline Visit (see [Section 9.3](#) for list of restricted meds), with the exception of UDCA in which subjects need to be on stable therapy for  $\geq 3$  months.

### 8.3 Exclusion Criteria

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

1. Presence of documented secondary sclerosing cholangitis (such as ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis) on prior clinical investigations
2. Small duct PSC
3. Presence of percutaneous drain or bile duct stent
4. History of cholangiocarcinoma or high clinical suspicion over dominant stricture within 1 year by MRCP/ERCP or clinical judgement
5. Ascending cholangitis within 60 days prior to Screening
6. Alcohol consumption greater than 21 units/week for males or 14 units/week for females (one unit of alcohol is ½ pint of beer [285 mL], 1 glass of spirits [25 mL] or 1 glass of wine [125 mL])
7. Prior or planned liver transplantation
8. Presence of alternative causes of chronic liver disease, including alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cirrhosis, autoimmune hepatitis
9. History of cirrhosis and/or hepatic impairment (Child-Pugh classes A, B and C) and/or hepatic decompensation including ascites, encephalopathy or variceal bleeding. Subjects who show evidence of significant worsening of hepatic function will be excluded
10. Subjects with evidence of cirrhosis, as determined by local transient elastography (TE; e.g., FibroScan<sup>®</sup>) values of  $\geq 13.0$  kPa, taken within the last 6 months. If TE has not been conducted within the 6 months prior to screening then one will be conducted during the screening period and can be used as the Baseline value
11. Moderate to Severe active IBD or flare in colitis activity within the last 90 days requiring intensification of therapy beyond Baseline treatment. Subjects with stable mild to moderate IBD, who are on treatment, are allowed provided they are stable for 3 months with 5-amino salicylic acid drugs or Azathioprine (allowed dose of azathioprine is 50-200 mg/day)
12. Use of oral prednisolone  $> 10$  mg/day, biologics and/or hospitalization for colitis within 90 days are disallowed
13. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT); above the allowed cut-offs, as determined by the Screening values:

- AST > 200 IU/L males and females
- ALT males > 250 IU/L and females > 200 IU/L

14. Total Bilirubin and Direct Bilirubin; above the allowed cut-offs, as determined by the Screening values:

- Total Bilirubin > 2.0 mg/dL
- Direct Bilirubin > 0.8 mg/dL

15. International normalized ratio (INR) > 1.3 in the absence of anticoagulants.

16. Immunoglobulin G4 (IgG4) > 4 × ULN at Screening or evidence of IgG4-related sclerosing cholangitis

[REDACTED]

[REDACTED]

34. Any other clinically significant disorders or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for the study or unable to comply with the dosing and protocol requirements

## 9.0 TREATMENTS

### 9.1 Treatments Administered

All eligible subjects will receive 150 mg CVC (n=25) daily for 24 weeks. CVC should be taken every morning with food.

### 9.2 Study Drug

#### 9.2.1 Investigational Product

Chemical Name:

[REDACTED]

Generic Name: Cenicriviroc mesylate

Abbreviated Name: CVC

Laboratory Designation:

[REDACTED]

Trade Name: Not applicable

[REDACTED]

#### 9.2.2 Packaging and Labeling

The study medication will be supplied, as described above, by Tobira and will be packaged in high-density polyethylene bottles containing 37 tablets per bottle with polyester coil, silica gel desiccant and induction sealed.

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 medication should be stored at controlled room temperature, [REDACTED] with transient excursions permitted to [REDACTED]. CVC tablets will continue to be monitored for stability at [REDACTED] recommended storage conditions.

#### 9.2.4 Study Drug Dispensing and Collection

Study medication (CVC) will be supplied in a bottle containing 37 tablets for each subject, which is sufficient for 28 days dosing. Study drug bottles will be assigned by site pharmacist or designated site personnel to study site personnel/subjects at Baseline, Week 4, Week 8, Week 12 and Week 16. At the week 16 visit 2 bottles will be given as the next study visit is Week 24. Subjects will be instructed to take 1 tablet of medication each day, in the morning,

with food. Unused medication and the medication bottle will be collected from each subject at each visit starting Week 4 until Week 24.

### ***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 medication. The investigator or designee must maintain records that document the following:

- Study medication 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 medications to the investigator or designee
- Destruction of returned and residual containers

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

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

Completed accountability records will be archived by the site. Study monitors will check drug accountability records and verify destruction of empty containers.

The investigator or designee will oversee destruction of any empty containers and residual study drug according to institutional standard operating procedures (SOPs). In the absence of an institutional SOP, the clinical research associate (CRA) will be responsible for ensuring that the drug is sent to an appropriate drug destruction facility. The CRA will verify drug accountability records and destruction at regular intervals throughout the study. A certificate of destruction will be provided to the CRA for all destroyed drug.

### ***9.2.6 Study Drug Administration***

Subjects will take 1 tablet of study treatment daily for 24 weeks of treatment. Subjects will be instructed to take the study treatment every morning with food.

All subjects will come into the clinic fasting and hold their daily dose on the day of each on-treatment clinic visit. Subjects will bring their study drug bottle to the clinic and take one dose of the study medication under witnessed dosing with food, after blood draws.

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 per day and should not discard any unused medication.


### 9.3 Prior and Concomitant Therapy

All medications (or treatments) other than study drug taken or received by the subject at any time during the study from Screening through the 4-Week Follow-up visit will be considered concomitant medications (or treatments). All concomitant medications and treatments must be recorded in the case report form (CRF). Any prior medication received within 28 days of the first dose of study drug will be recorded in the CRF. Concomitant treatments that are required to manage a subject's medical condition during the trial will also be recorded in the CRF.

Subjects will be allowed to continue their usual standard-of-care medications that are not specifically excluded by the protocol. Required dose modifications of medications not excluded by the protocol may be performed per the clinical judgement of the investigator. The detailed list of disallowed study medications and the list of medications that are allowed but with specific restrictions are provided in Appendix [20.4](#).

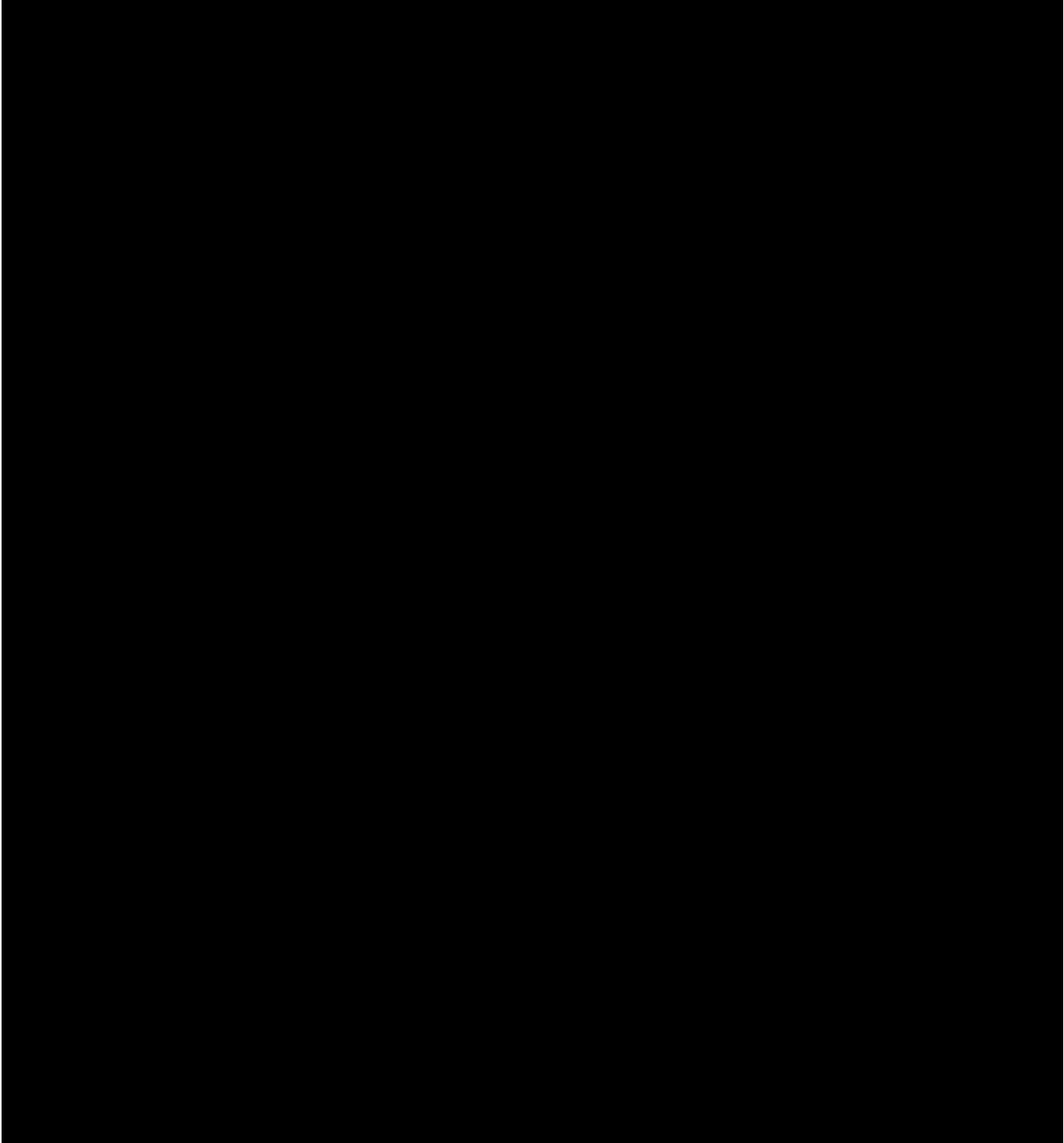
The following classes of medications are disallowed during the study:

- [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
  - [REDACTED]
- [REDACTED]
- [REDACTED]



In instances where a disallowed medication is initiated prior to discussion with the medical monitor and/or Sponsor, the investigator must notify Tobira as soon as he/she is aware of the use of the excluded medication to discuss the subject's continued participation in the study.

Medications that are commonly used for IBD or for PSC symptoms are listed below. The detailed list of disallowed study medications and the list of medications that are allowed but with specific restrictions are provided in Appendix [20.4](#).



#### **9.4 Additional Restrictions and Precautions**

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

Although no cases of photosensitivity reactions have been reported in completed clinical studies, previous nonclinical studies indicated that CVC and/or its metabolites have an

affinity for melanin. Therefore, additional studies were conducted with results indicating that CVC did not demonstrate phototoxic potential in neutral red uptake phototoxicity in BALB/c 3T3 mouse fibroblasts. As a measure of caution, subjects should be advised to avoid undue direct ultraviolet (UV) exposure from natural sunlight or tanning beds. These measures include wearing sun-protective clothing and sunglasses and using a UV-A and UV-B combination sunscreen (sun protection factor at least 15).

## 9.5 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. Subjects who miss doses must be counseled on the importance of adhering to their daily dosing schedule.

## 10.0 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 (e.g., weight lifting, strenuous yard work, intensive exercise workouts) for 48 hours prior to study visits and laboratory evaluations.

For IBD subjects only: Eligible subjects will be required to complete a diary daily to assess stool frequency and blood in the stool (Partial Mayo Risk score), daily. In addition, the diary will include a question regarding abdominal pain in order to assess if the subject develops any significant increase in abdominal pain. If a subject exceeds a Partial Mayo Risk score of 4 at any time, by investigator assessment of patient diary as well as subject evaluation, then the subject will be reevaluated for his or her IBD at the clinical research site. Should subjects experience an increase in abdominal pain, stool frequency or blood in their stool between visits, they will be instructed to contact the site immediately for clinical assessment for their IBD.

The principal investigator or delegate will be instructed to inquire about abdominal pain at each study visit. As with all adverse events, any abdominal pain will be assessed for severity and causality by the investigator in the eCRF, per Section 11.4.

### 10.1 Screening Visit

Prior to any clinical procedures and evaluations, written signed informed consent must be obtained. Screening is to occur approximately 6 weeks before the Baseline visit (see Section 10.2).

Subjects who do not meet all eligibility criteria at Screening will be allowed to rescreen once. However, if a subject fails to meet eligibility criteria upon rescreen, he or she will remain ineligible for the study.

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

■ [REDACTED]

[REDACTED]

### 10.2 Baseline Visit (Day 1)

Subjects who have signed the ICF and meet all the eligibility criteria (see Sections [8.2](#) and [8.3](#)) will be enrolled in the study. If subjects are deemed eligible once results from the Screening visit are received, Baseline visit can take place immediately or approximately within 6 weeks after the Screening visit.

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- █ [REDACTED]
- █ [REDACTED]

#### 10.4 4-Week Follow-up (Week 28, Day 196)

Subjects will undergo follow-up evaluations approximately 4 weeks after the last dose of study drug (Week 28). Subjects who discontinue study drug prior to completion of 24 weeks of treatment will be required to return for an Early Discontinuation Visit within 48 hours after the last dose of study drug and this 4-week Follow-up Visit.

The following procedures and assessments for the 4-Week Follow-up Visit will be conducted:

- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]

#### 10.5 Early Discontinuation Visit

Subjects may discontinue study treatment at any time for any reason (see Section 10.7).

For subjects who discontinue study drug prior to having completed 24 weeks of treatment, every effort should be made to ensure that they return for Early Discontinuation procedures within 48 hours after discontinuing study drug. The procedures and assessments for Early Discontinuation will include all assessments in Section 10.3 and in the Schedule of Assessments in Section 20.1.

After the Early Discontinuation Visit, these subjects will be required to return to the clinic 4 weeks after completion of the Early Discontinuation Visit for a Follow-up Visit (Section 10.4).

#### 10.6 Missed Scheduled Visits

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



## 10.7 Criteria for Discontinuation of Study Treatment



Study medication must also be discontinued in the following instances:

- Unacceptable toxicity, as defined in the toxicity management section of the protocol (see Section 11.4.6), or which, in the judgment of the investigator, compromises the ability to continue study-specific procedures, or is considered to not be in the subject's best interest
- Acute viral hepatitis Types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy
- Subject requests to discontinue treatment for any reason
- Pregnancy during the course of the study
- Discontinuation of the study at the request of Tobira, Regulatory Agency or Institutional Review Board (IRB) / Research Ethics Board (REB)

If subjects discontinue from the study for reasons other than safety, replacement subjects will be considered.

## **11.0 STUDY ASSESSMENTS**

### **11.1 Demographic and Other Pretreatment Assessments**

After written informed consent is obtained, demographic data and a complete medical and medication history will be collected at the Screening Visit. A complete physical examination, including measurements of height and body weight will be performed. Medical history will be updated until the first dose of study medication. All AEs will be recorded from the time of informed consent and throughout the study, regardless of apparent causality from use of the study treatment. Medications taken before the first dose of study drug will be recorded as prior medications.

### **11.2 Assessments of Efficacy**

This study will evaluate the effects of CVC in adult subjects with PSC. [REDACTED]

### **11.3 Assessments of Pharmacokinetics**

### **11.4 Assessments of Safety**

AEs will be assessed at each visit.

#### ***11.4.1 Adverse Events and Serious Adverse Events***

##### **11.4.1.1 Definitions**

##### **11.4.1.1.1 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.

#### 11.4.1.1.2 Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as any AE 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.

#### 11.4.1.1.3 Suspected Adverse Reaction

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

#### 11.4.1.1.4 Unexpected Adverse Event or Reaction

An AE 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.

#### 11.4.1.1.5 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 11.4.1.1.9), it must be reported as such (see Section 11.4.1.5).

#### 11.4.1.1.6 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 test) 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 11.4.2.2 for details regarding the management and monitoring of laboratory abnormalities of interest.

#### 11.4.1.1.7 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.

#### 11.4.1.1.8 Overdose

Tobira also considers the occurrence of overdose (regardless of adverse outcome) as an event that must be reported as an AE. An overdose is defined as a subject's report of taking more than 1 tablet of study medication (i.e., more than 1 tablet per day of CVC). Overdose of any concomitant medication without any signs and symptoms will not be considered an AE. For reporting purposes, overdose will be considered an SAE only if any of the seriousness criteria are met (see definition in Section 11.4.1.1.9).

#### 11.4.1.1.9 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 (i.e., 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.)

#### 11.4.1.2 Adverse Event Recording

AEs fall into the categories of “nonserious” and “serious.” From the time of informed consent and throughout the study, all AEs must be recorded in the CRF, regardless of apparent causality from use of the study treatment. The AE 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.

The following information should be captured for all AEs: date of onset and end date or outcome (e.g., 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 medication and treatment required for the AE, cause of the event (if known), and information regarding the resolution/outcome.

AEs classified as serious must be recorded on the appropriate SAE reporting tool and reported to Tobira using expeditious handling to comply with regulatory requirements (see Section 11.4.1.5).

#### 11.4.1.3 Adverse Event Classification

[REDACTED]

- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]
- | [REDACTED]

[REDACTED]

[REDACTED]

- | [REDACTED]
- | [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### 11.4.1.4 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.

#### 11.4.1.5 Reporting of Serious Adverse Events

Tobira is required to expedite to regulatory authorities reports of SAEs, serious ADRs, or 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 Tobira 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 ICF to within 28 days following discontinuation of study treatment, regardless of relationship to the study treatment, must be reported within 24 hours to the contact below:

#### SAE Contact

##### Primary Contact:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

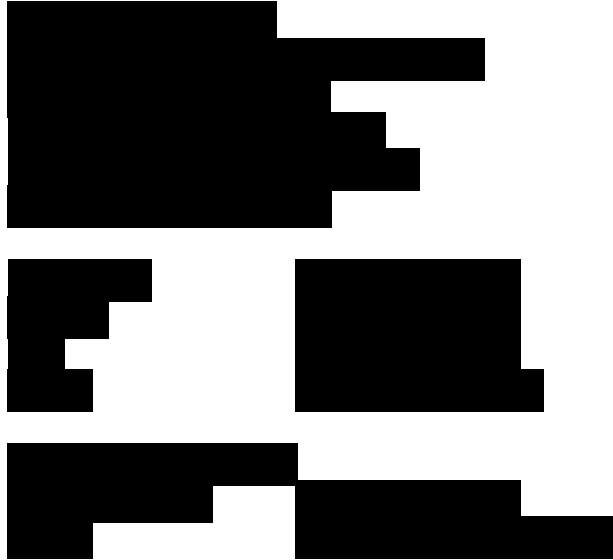
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**Secondary Contact:**



The required SAE information must be completed on the SAE Form (MedWatch or CIOMS). Tobira may request additional information from the investigator to ensure the timely completion of accurate safety reports.

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 CRF 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 Tobira to determine how the event should be documented and reported.

In case of emergency, contact the Tobira medical monitor (see Section 11.4.1.5 for contact information).

The Investigator 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 European Union Clinical Trials Directive (2001/20/EC), Tobira 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.

**11.4.1.6 Follow-up of AEs and SAEs**

AEs (including SAEs) will be collected from the time of informed consent, throughout the treatment period, until 28 days after the last dose of study medication 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.

#### 11.4.1.7 Pregnancy

If a 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 Tobira 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 Tobira Drug Safety.

All pregnancies that occur during the study should be reported using the Pregnancy Report Form, which should be faxed to Tobira Drug Safety within 24 hours of first knowledge by the investigator. Monitoring of the subject should continue until the conclusion of the pregnancy. The outcome should be reported to Tobira Drug Safety using the Pregnancy Outcome Report Form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Tobira Drug Safety. Pregnancies that occur more than 28 days after the subject has discontinued study drug do not require monitoring.

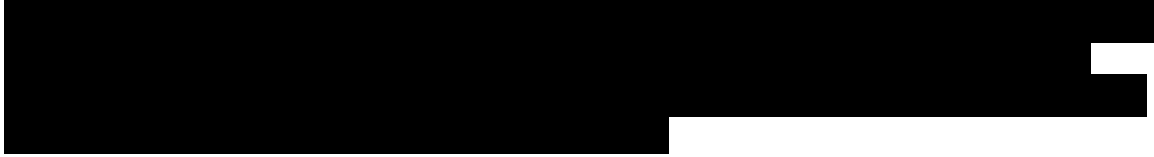
### ***11.4.2 Laboratory Assessments***

#### 11.4.2.1 Measurement of Laboratory Assessments

A central laboratory will perform all clinical safety laboratory tests. Urine drug screens will also be analyzed at the central laboratory. Urine pregnancy tests will be performed at the site using a dipstick method, except at Screening where a serum pregnancy test will be performed. If there is a positive urine pregnancy test while on-study, a serum pregnancy test will be conducted by the central lab.

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





A complete list of all laboratory tests is provided in Appendix [20.5](#).

#### 11.4.2.2 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 CRF. See Section [11.4.1.1.6](#) for a definition of clinically significant laboratory abnormality. For management of subjects with elevated liver tests, please refer to Section [11.4.6.4](#).

#### ***11.4.3 Vital Signs***

Vital sign measurements (systolic and diastolic blood pressure, temperature, heart rate, and respiration rate) will be taken at each visit. For subjects who discontinue study medication early, vital signs will be measured at the Early Discontinuation Visit within 48 hours of stopping study medication. Vital signs will be performed with the subject in the sitting position after 5 minutes of rest.

#### ***11.4.4 Electrocardiogram***

A 12-lead ECG will be taken at the Baseline/Day 1 Visit, and at Week 24. ECGs will be performed with the subject in the supine position after 5 minutes of rest.

#### ***11.4.5 Physical Examination***

A complete physical examination will be performed at the Screening 1 Visit and the Baseline/Day 1 Visit. A symptom-directed physical examination will be performed, as needed, at the Screening 2 Visit, at all On-treatment Visits, at the Early Discontinuation Visit within 48 hours of stopping study medication, and at the 4-Week Follow-up Visit. The complete physical examination will include (but not limited to) the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver and spleen); extremities; lymph nodes; and a brief neurological exam. Abbreviated symptom-directed physical examinations will target signs and symptoms; any abnormal findings that are reported as AEs will be recorded in the CRF.

#### ***11.4.6 Toxicity Management***

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



[Redacted text block]

#### 11.4.6.4 Management of Subjects with Elevated ALP, ALT, AST or Bilirubin

If a subject is *asymptomatic* but experiences clinically significant elevations of liver transaminases or Bilirubin, subjects must repeat physical examination and laboratory evaluation within 48-72 hours for repeat testing and close monitoring, preferably at the clinical research site or alternately at a local laboratory.

[REDACTED]

- 1 [REDACTED]

- 2 [REDACTED]

- 3 [REDACTED]

For confirmed elevations of above parameters, the subject must interrupt study drug. Close monitoring of study subjects includes:

- 1 [REDACTED]

- 2 [REDACTED]

- 3 [REDACTED]

- 4 [REDACTED]

- 5 [REDACTED]

- 6 [REDACTED]

- 7 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- 1 [REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

**11.5 Biomarker Analysis**

Serum samples will be stored at the central lab for potential evaluation of biomarkers of interest at Baseline and at Weeks 12 and 24.

**11.6 Assessments of Medication Adherence**

Drug accountability through the assessment of pill counts will be performed by clinic staff at each on-treatment evaluation visit.

[REDACTED]

[REDACTED]

## 12.0 STATISTICS

### 12.1 Sample Size and Power

This is a single arm, open label, PoC study in 25 adult subjects with PSC; and for which each patient will serve as their own control when observing ALP relative to Baseline. With respect to a potential range of -20% for worsening to 80% for improvement in percent ALP change from Baseline to 24 weeks, a reasonably applicable standard deviation is 25%. Thus, 0.80 power would apply for the two-sided 95% confidence interval for mean percent change from Baseline to 24 weeks to have its lower limit exceed 15% if the true mean percent change from Baseline to 24 weeks is at least 30%. Also, for a dichotomous responder criterion such as either a 50% ALP decrease from Baseline to 24 weeks or an ALP decrease to 1.5xULN at 24 weeks, 0.80 power would apply for the two-sided 95% confidence interval to have its lower limit exceed 10% if the true responder percentage is at least 40%. Thus, in this sense, a sample size of 25 is sufficient to determine if there is a positive signal in ALP during CVC treatment.

### 12.2 General Considerations

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term “descriptive statistics” refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum (with quartiles, 10-th percentile, and 90-th percentile when useful) for continuous data and frequencies and percentages for categorical data.

#### 12.2.1 Analysis Populations

**Intention to Treat (ITT) Population:** The ITT population will include all subjects enrolled to receive treatment.

**Per Protocol (PP) Population:** The PP population will include all subjects who are enrolled, have no contraindicated concomitant medications, have adequate study medication compliance.

**Safety Population:** The safety population will include all subjects who received at least one dose of study drug. This population will be used for all safety analyses

#### 12.2.2 Handling of Missing Data

Data will be analyzed as recorded. There will be no imputations conducted for missing data. A summary of missing data will be included in the final statistical report

#### 12.2.3 Subject Replacement

If a subject discontinues from the study for reasons other than safety, a replacement subject will be considered and included in the study analysis.

### 12.3 Subject Disposition

Subject disposition will be presented for all subjects. The number of subjects who completed the study and discontinued from the study will be provided. The reasons for early discontinuation also will be presented.

## 12.4 Efficacy

### 12.4.1 Efficacy Endpoint

The primary efficacy endpoint for this study is the percent change from Baseline through Week 24 in serum alkaline phosphatase. [REDACTED]

### 12.4.2 Methods of Analysis for Primary and Secondary Efficacy Endpoints

Percent changes in ALP from Baseline will be summarized using descriptive statistics for the respective pre-treatment and on-treatment visits. [REDACTED]

## 12.5 Safety

### 12.5.1 Safety Endpoints

Safety endpoints include:

- Evaluation of the safety and tolerability through 24 weeks of treatment in adult PSC subjects
- Evaluation of AEs, clinical laboratory tests, physical exam and 12-lead ECG.

## ***12.5.2 Methods of Analysis for Safety Endpoints***

### **12.5.2.1 Adverse Events**

AEs will be tabulated by the MedDRA preferred term and system-organ classification. The occurrence of TEAEs will be summarized by treatment group using MedDRA preferred terms, system organ classifications, and severity (see Sections [11.4.1.3](#) and [11.4.1.4](#)).

All AEs will be listed for individual subjects showing both verbatim and preferred terms. Separate summaries of treatment-emergent SAEs and TEAEs related to study drug will be generated.

Any event reported on the CRF that occurs on or after the initiation of study drug is defined as treatment-emergent. Additionally, it is assumed that an AE that was reported to have started on Day 1 without an associated onset time may have occurred after the initiation of study drug. Hence, AEs occurring on Day 1 with no associated onset time are assumed to be treatment-emergent.

### **12.5.2.2 Clinical Laboratory Tests**

Descriptive summaries of clinical laboratory results will be presented by study visit. Laboratory abnormalities will be graded according to NCI CTCAE version 4.03 (see Appendix [20.2](#)). The number and percentage of subjects experiencing treatment-emergent graded toxicities will be summarized by treatment group and severity grade. Laboratory toxicity shifts from Baseline to post-Baseline assessments will be summarized by treatment group. Changes from Baseline in laboratory tests will be summarized for each treatment group.

### **12.5.2.3 Physical Examination and Vital Signs**

Any abnormal findings that are considered clinically significant in the opinion of the investigator will be recorded as AEs or be captured as medical history, if already present at Screening.

Descriptive summaries of vital signs will be presented by study visit. Descriptive summaries of quantitative changes in vital signs will be presented by treatment group and study visit. Vital sign results will be reviewed for clinically notable abnormalities, according to predefined criteria, and adverse changes will be summarized.

#### **12.5.2.3.1 Electrocardiograms**

ECG results will be reviewed locally for clinically notable abnormalities according to predefined criteria. Patients exhibiting Grade 3 or 4 PR or QTc interval will be summarized.

#### **12.5.2.3.2 Prior and Concomitant Medications**

Prior and concomitant medications will be mapped to 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.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



## **13.0 QUALITY CONTROL AND QUALITY ASSURANCE**

### **13.1 Sponsor Audits**

During the study, individuals from the Tobira 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 Tobira's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the investigator will be contacted by Tobira 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 CRFs 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 CRFs and other study-related documents. The investigator must immediately notify Tobira when contacted by any regulatory authority for purposes of conducting an inspection.

## **14.0 ETHICS AND PROTECTION OF HUMAN SUBJECTS**

### **14.1 Compliance Statement**

The investigator agrees to conduct the study in compliance with the protocol, ICH E6 Good Clinical Practice (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 Tobira 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 Tobira 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 Tobira 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 (e.g., 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, Tobira 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 Tobira.

When Tobira 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 Tobira.

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 Tobira 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 Tobira or designee. Tobira or designee must review and approve all changes to site-specific ICFs.

The consent form must include a statement that Tobira 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 Tobira are responsible for ensuring that sensitive information is handled in accordance with local requirements (e.g., Health Insurance Portability and Accountability Act). 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 Tobira. Only the subject number and subject initials will be recorded in the CRF, and if the subject name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Tobira. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of Tobira, 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 Tobira 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 Tobira and retain one copy for the site study regulatory file.

## **15.0 DATA HANDLING AND RECORD KEEPING**

### **15.1 Data Management Responsibilities**

All CRF data will be entered into a validated database. Laboratory data will be received as [REDACTED] datasets from the central laboratory (or data received in a format that can be converted to [REDACTED]). The laboratory data will be reconciled against the blood and urine collection eCRFs in the database. The laboratory data [REDACTED] datasets along with the [REDACTED] datasets created from the EDC data will be provided to the statisticians as needed.

All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of Tobira 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 paper CRFs in which to record all the protocol-specified data for each subject in this study. Entries made in the CRF must be verifiable against source documents, or in certain circumstances as directed by Tobira, entries will have been directly entered into the CRF; in such cases, the entry in the CRF will be considered as the source data. Data reported in the CRF 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 CRF entries and will sign and date the designated pages in each subject's CRF, verifying that the information is true and correct.

Queries generated by Data Management at [REDACTED] will be sent to the study site for resolution. The investigator is responsible for the review and approval of all responses to CRF 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 Tobira. The investigator must notify Tobira in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, Tobira 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 CRF 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. Tobira will retain the original paper CRF data and audit trail.

### ***15.2.3 Study Monitoring and Access to Source Documents***

Qualified representatives of Tobira or its designees (“study monitors”) will monitor the study according to a predetermined monitoring plan. Monitoring visits provide Tobira with the opportunities to do the following:

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

The investigator must allow the study monitors to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each subject in the study. The CRFs 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 Tobira, at each monitoring visit.

The study monitor will review the various records of the study (CRFs, subject medical and laboratory records, and other pertinent data). The study monitor will verify the CRF 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.

[REDACTED]

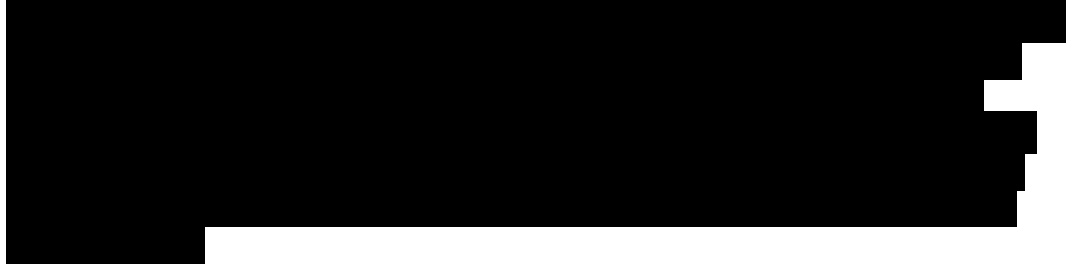
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## 17.0 REFERENCES

1. Hirschfield GM, Karlsen TH, Lindor KD, et al. Primary sclerosing cholangitis. *Lancet*. 2013;382(9904):1587-99.
2. Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of primary sclerosing cholangitis. *Hepatology*. 2010;51(2):660-78.
3. Eaton JE, Talwalkar JA, Lazaridis KN, et al. Pathogenesis of Primary Sclerosing Cholangitis and Advances in Diagnosis and Management. *Gastroenterology*. 2013;145(3):521-36.
4. Fiorotto R, Scirpo R, Trauner M, et al. Loss of CFTR affects biliary epithelium innate immunity and causes TLR4-NF- $\kappa$ B-mediated inflammatory response in mice. *Gastroenterology*. 2011;141(4):1498-508.
5. Spirli C, Nathanson MH, Fiorotto R, et al. Proinflammatory cytokines inhibit secretion in rat bile duct epithelium. *Gastroenterology*. 2001;121(1):156-69.
6. Aron JH, Bowlus CL. The immunobiology of primary sclerosing cholangitis. *Semin Immunopathol*. 2009;31(3):383-97.
7. Harada K, Nakanuma Y. Innate immunity in the pathogenesis of cholangiopathy: a recent update. *Inflammation & Allergy-drug targets*. 2012;11(6):478-83.
8. Priester S, Wise C, Glaser SS. Involvement of cholangiocyte proliferation in biliary fibrosis. *World J Gastrointest Pathophysiol*. 2010;1(2):20-37.
9. Lee SJ, Kim KH, Park KK. Mechanisms of fibrogenesis in liver cirrhosis: The molecular aspects of epithelial-mesenchymal transition. *World J Hepatol*. 2014;6(4):200-16.
10. Omenetti A, Porrello A, Jung Y, et al. Hedgehog signaling regulates epithelial-mesenchymal transition during biliary fibrosis in rodents and humans. *J Clin Invest*. 2008;118(10):3331-42.
11. Bambha K, Kim WR, Talwalkar J, et al. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community. *Gastroenterology*. 2003;125(5):1364-9.
12. Boonstra K, Weersma RK, van Erpecum KJ, et al; EpiPSCPBC Study Group. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology*. 2013;58(6):2045-55.
13. Molodecky NA, Kareemi H, Parab R. Incidence of primary sclerosing cholangitis: a systematic review and meta-analysis. *Hepatology*. 2011;53(5):1590-9.
14. Kaplan GG, Laupland KB, Butzner D, et al. The burden of large and small duct primary sclerosing cholangitis in adults and children: a population-based analysis. *Am J Gastroenterol*. 2007;102(5):1042-9.

15. Weisner RH, Grambsch PM, Dickson ER. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. *Hepatology* 1989;10(4):430-6.
16. Ali AH, Carey EJ, Lindor KD. Current research on the treatment of primary sclerosing cholangitis. *Intractable Rare Dis Res.* 2015;4(1):1-6.
17. Broome U, Olsson R, Lööf L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut.* 1996; 38:610-15.
18. Tischendorf J, Hecker H, Krüger M, et al. Characterization, Outcome, and Prognosis in 273 Patients with Primary Sclerosing Cholangitis: A Single Center Study. *Am J Gastroenterology* 2007; 102:107-14.
19. Lindor KD, Kowdley KV, Luketic VA. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology.* 2009;50(3):808-14.
20. Beuers U, Spengler U, Kruis W, et al. Ursodeoxycholic acid for treatment of primary sclerosing cholangitis: a placebo-controlled trial. *Hepatology.* 1992;16(3):707-14.
21. Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. *NEJM.* 1997;336(10):691-5.
22. Mitchell SA, Bansi DS, Hunt N, Von Bergmann K, Fleming KA, Chapman RW. A preliminary trial of high-dose ursodeoxycholic acid in primary sclerosing cholangitis. *Gastroenterology.* 2001;121:900–907.
23. Olsson R, Boberg KM, de Muckadell OS. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. *Gastroenterology.* 2005;129(5):1464-72.
24. Lindstrom L, Hultcrantz R, Boberg KM, et al. Association Between Reduced Levels of Alkaline Phosphatase and Survival Times of Patients With Primary Sclerosing Cholangitis. *Clinical Gastro and Hepatol.* 2013;11(7):841-46.
25. Eaton JE, Silveira MG, Pardi DS, et al. High-Dose Ursodeoxycholic Acid Is Associated With the Development of Colorectal Neoplasia in Patients With Ulcerative Colitis and Primary Sclerosing Cholangitis. *Am J Gastroenterology.* 2011;106:1638-45.
26. Beuers U, Boberg K, Chapman R, et al. EASL Practice Guidelines. *J Hepatology.* 2009;51:237–67.
27. Ponsioen CY, Chapman RW, Chazouillères O. Surrogate endpoints for clinical trials in primary sclerosing cholangitis; review and results from an International PSC Study Group consensus process. *Hepatology.* 2015 Sep 29. doi: 10.1002/hep.28256[Epub ahead of print].

28. Rupp C, Rossler A, Halibasic E. Reduction in alkaline phosphatase is associated with longer survival in primary sclerosing cholangitis, independent of dominant stenosis. *Alimentary Pharmacology and Therapeutics*, 2014;40(11-12):1291-301.
29. Stanich PP, Einar Björnsson, Andrea A. Gossard. Alkaline phosphatase normalization is associated with better prognosis in primary sclerosing cholangitis. *Digestive Liver Disease*. 2011;43(4):309-13.
30. Harada K, Nakanuma Y. Innate Immunity in the Pathogenesis of Cholangiopathy: A Recent Update. *Inflammation & Allergy - Drug Targets*;11(6):478-483.
31. Marra F, Romanelli RG, Giannini C, et al. Monocyte chemoattractant protein-1 as a chemoattractant for human hepatic stellate cells. *Hepatology*. 1999;29(1):140-8.
32. Zimmermann HW, Tacke F. Modification of chemokine pathways and immune cell infiltration as a novel therapeutic approach in liver inflammation and fibrosis. *Inflamm Allergy Drug Targets*. 2011;10(6):509-36.
33. Mitchell C, Couton D, Couty JP, et al. Dual role of CCR2 in the constitution and the resolution of liver fibrosis in mice. *Am J Pathol*. 2009;174:1766-1775.
34. Schwabe RF, Bataller R, Brenner DA. Human hepatic stellate cells express CCR5 and RANTES to induce proliferation and migration. *J Physiol Gastrointest Liver Physiol* 2003;285:G949-G958.
35. Saiman Y, Friedman S. The role of chemokines in acute liver injury. *Frontiers in Physiology*. 2012;3:213.
36. Seki E, De Minicis S, Gwak GY, et al. CCR1 and CCR5 promote hepatic fibrosis in mice. *J Clin Invest*. 2009;119:1858-70.
37. Seki E, de Minicis S, Inokuchi S. CCR2 promotes hepatic fibrosis in mice. *Hepatology*. 2009;50(1):185-197.
38. Miura K, Yang L, Rooijen NV, et al. Hepatic recruitment of macrophages promotes nonalcoholic steatohepatitis through CCR2. *Am J Physiol Gastrointest Liver Physiol*. 2012;302:G1310-G1321.
39. Tabibian JH, O'Hara SP, Splinter PL, et al. Cholangiocyte senescence by way of N-ras activation is a characteristic of primary sclerosing cholangitis. *Hepatology*. 2014; 59(6):2263-75.
40. Tsuneyama K, Harada K, Yasoshima M, et al. Monocyte chemoattractant protein-1, -2, and -3 are distinctively expressed in portal tracts and granulomata in primary biliary cirrhosis: implications for pathogenesis. *Journal of Pathology*. 2001;193(1):102-09.

41. Nakken KE, Nygård S, Haaland T, Berge KE, Arnkvaern K, Ødegaard A, Labori KJ, Raeder MG. Multiple inflammatory-, tissue remodelling- and fibrosis genes are differentially transcribed in the livers of Abcb4 (-/-) mice harbouring chronic cholangitis. *Scand J Gastroenterol.* 2007;42:1245–1255
42. Henckaerts L, Pierik M, Joossens M. Mutations in pattern recognition receptor genes modulate seroreactivity to microbial antigens in patients with inflammatory bowel disease. *Gut.* 2007;56(11):1536-42.
43. Henckaerts L, Fevery J, Van Steenberghe W, et al. CC-type chemokine receptor 5-Delta32 mutation protects against primary sclerosing cholangitis. *Inflamm Bowel Dis.* 2006;12(4):272-7.
44. Dries S, Buis C, Adelmeijer J, et al. The combination of primary sclerosing cholangitis and CCR5-Δ32 in recipients is strongly associated with the development of nonanastomotic biliary strictures after liver transplantation. *Liver International* 2011;31(8):1102–09.
45. Receptor binding properties of TAK 652, a small molecular weight CCR5 antagonist. Takeda Chemical Industries, Ltd., Report No. TAK-652/00045, Jun 2003.
46. Preclinical testing of the CCR5/CCR2 dual antagonist Cenicriviroc (TBR-652). Study No. 652-9-1015 (Interim Report), 24 Mar 2014.
47. In vivo efficacy study of cenicriviroc in STAM model of non-alcoholic steatohepatitis. Study 652-9-1002, Report No. SR\_MNP010-1209-1, 29 Oct 2013.
48. Lefebvre E, Hashiguchi T, Jenkins H, et al. Anti fibrotic and anti-inflammatory activity of the dual CCR2 and CCR5 antagonist cenicriviroc in a mouse model of NASH. *Hepatology* 2013;58(S1):221A-222A.
49. Activity of cenicriviroc in a rat model of thioacetamide-induced liver fibrosis and cirrhosis. Study No. 652-9-1003, 24 Dec 2013.
50. Hong F, Chou H, Friedman SL. Significant anti-fibrotic activity of cenicriviroc, a dual CCR2/CCR5 antagonist, in a rat model of thioacetamide-induced liver fibrosis and cirrhosis. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013). Washington, DC, November 1-5, 2013. Abstract LB-7.
51. Richards TL. Dose-dependent effects of cenicriviroc on renal biomarkers and fibrosis in unilateral ureteral occluded (UUO) mice. Study No. 652-9-1006, 28 Feb 2014.
52. Krenkel O, Mossanen JC, Ergen C, et al. CCR2+ infiltrating monocytes promote acetaminophen-induced acute liver injury - therapeutic implications of inhibiting CCR2 and CCL2. *J Hepatol.* 2015;62:S206.

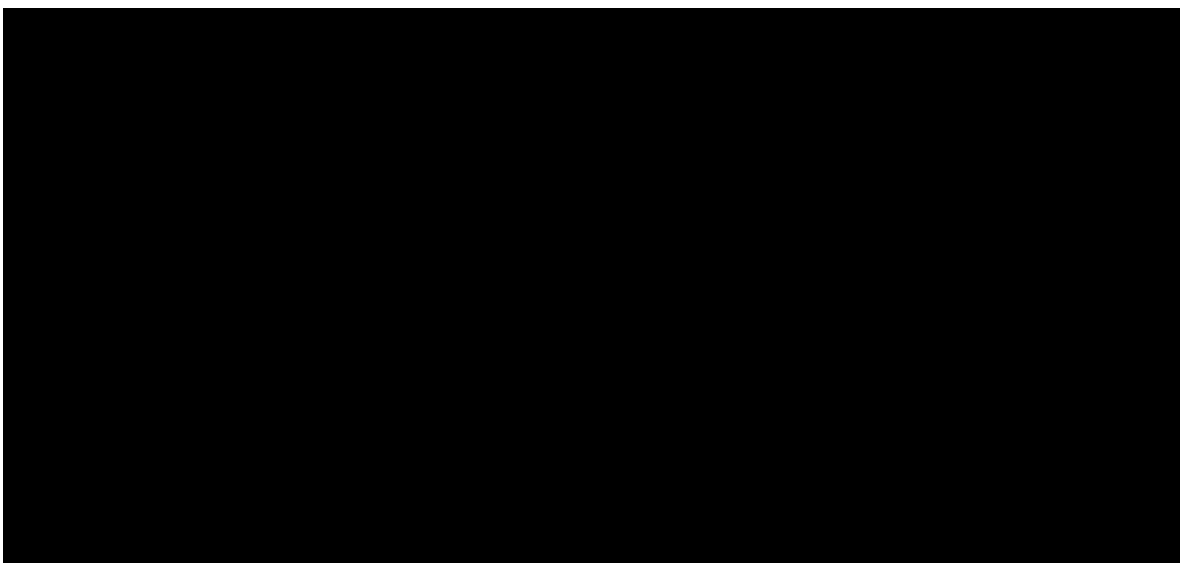
53. Krenkel O, Püngel T, Mossanen J, et al. Dual CCR2/CCR5 antagonist cenicriviroc leads to potent and significant reduction in proinflammatory CCR2+ monocyte infiltration in experimental acute liver injury. Presented at: The Liver Meeting®; Nov 17, 2015; San Francisco, CA, USA
54. Prophylactic Effects of Cenicriviroc on Bile Duct Ligation Induced Liver Injury and Hepatic Fibrosis; Study number 652-9-1030, Plato Biosciences, Tobira study report, October 2015.
55. Cenicriviroc Mesylate. CVC (TBR-652) For the Treatment of Non Alcoholic Steatohepatitis (NASH) in Subjects with Liver Fibrosis, Investigator's Brochure, Edition 1. Tobira Therapeutics, Inc., dated 8 August 2014.
56. Cai Z, Christianson AM, Stahle L, et al. Reexamining transaminase elevation in Phase I clinical trials: the importance of Baseline and change from Baseline. *Eur J Clin Pharmacol.* 2009;65:1025-35.
57. Sandler NG, Wand H, Roque A, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis.* 2011;203:780–90.
58. Sandler NG, Koh C, Roque A, et al. Host response to translocated microbial products predicts outcomes of patients with HBV or HCV infection. *Gastroenterol.* 2011;141:1220-30.
59. Ogawa Y, Imajo K, Yoneda M, et al. Soluble CD14 Levels Reflect Liver Inflammation in Patients with Nonalcoholic Steatohepatitis. *PLoS ONE* 2013;8(6):e65211. doi:10.1371/journal.pone.0065211.
60. Harte A, da Silva N, Creely S, et al. Elevated endotoxin levels in non-alcoholic fatty liver disease. *J Inflamm.*2010;7:15-24.
61. He H, Mennone A, Boyer JL, and Cai SY. Combination of retinoic acid and ursodeoxycholic acid attenuates liver injury in bile duct ligated rats and human hepatic cells. *Hepatology.* 2011;53(2): 548–557.
62. Fickert P, Pollheimer MJ, Beuers U, et al. Characterization of animal models for primary sclerosing cholangitis (PSC). *J Hepatol.* 2014;60(6):1290-303.
63. Liedtke C, Luedde T, Sauerbruch T, et al. Experimental liver fibrosis research: update on animal models, legal issues and translational aspects. *Fibrogenesis Tissue Repair.* 2013;6:19.
64. FDA Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009. Available at <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>

## **18.0 SPONSOR'S SIGNATURE PAGE**

### **PERSEUS: A Phase 2 Proof of Concept Study Investigating the Preliminary Efficacy and Safety of Cenicriviroc in Adult Subjects with Primary Sclerosing Cholangitis (PSC)**

**Protocol Issue Date: 14 June 2016**  
**Amendment 3**

I have reviewed and approved the attached version, cited above, of Protocol 652-205.



## 19.0 INVESTIGATOR'S SIGNATURE PAGE

### **PERSEUS: A Phase 2 Proof of Concept Study Investigating the Preliminary Efficacy and Safety of Cenicriviroc in Adult Subjects with Primary Sclerosing Cholangitis (PSC)**

**Protocol Issue Date:** 14 June 2016  
**Amendment 3**

I have read, understand, and agree to follow the attached version, cited above, of Protocol 652-205.

\_\_\_\_\_  
Principal Investigator Name (Print)

\_\_\_\_\_  
Signature

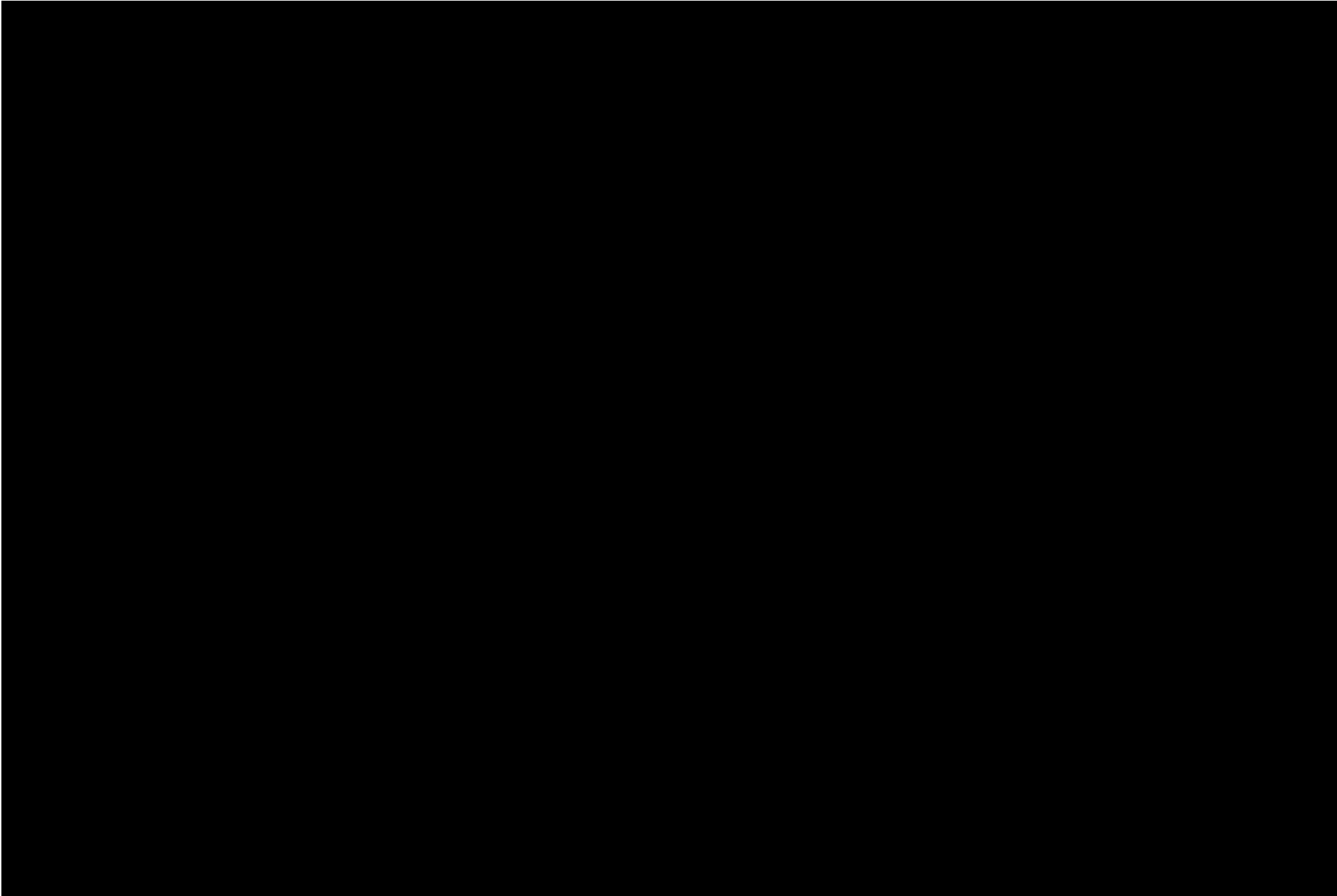
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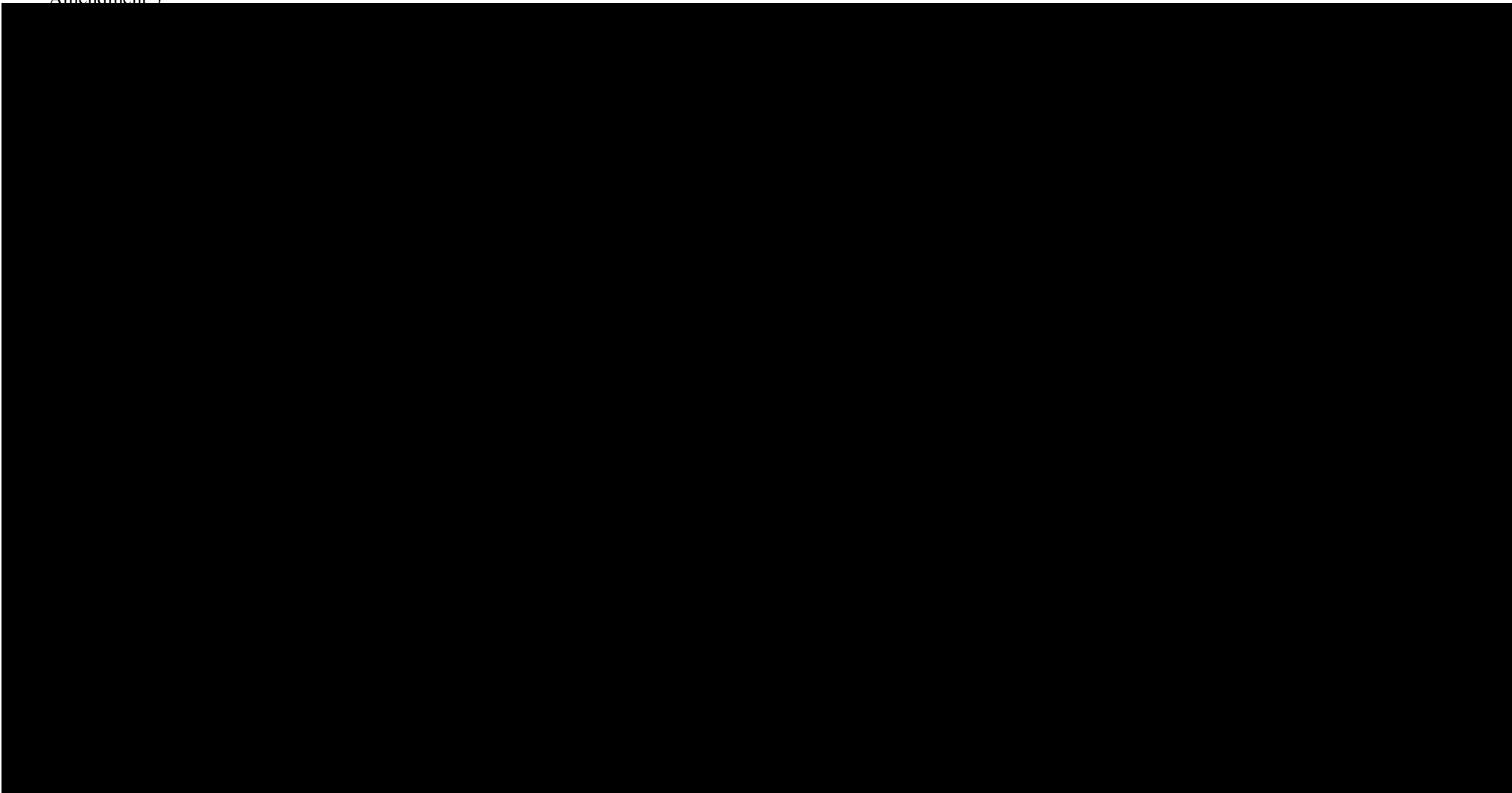
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## **20.0 APPENDICES**



**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](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 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 (e.g., 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 AE 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**

#### ***For Female Study Subjects of Child-Bearing Potential and For Male Study Subjects with Female Partners***

The following methods have been determined to be more than 99% effective (failure rate < 1% per year, when used consistently and correctly) (Trussell 2004) and are permitted under this protocol:

- Complete abstinence from sexual intercourse if this is the subject's usual and preferred lifestyle
- Dual method of contraception:
  - Condom with spermicide in conjunction with use of an intrauterine device
  - Condom with spermicide in conjunction with use of a diaphragm
  - Condom with birth control patch or vaginal ring\*
  - Condom with oral, injectable, or implanted contraceptives\*
- Tubal ligation or vasectomy (surgical sterilization\*\*)

\* Note: Subjects who are using hormonal contraceptives should be instructed to use an additional contraceptive measure during the study (see above for other methods).

\*\* *Note:* For the purpose for this study protocol, "surgical sterilization" also includes hysterectomy and/or bilateral oophorectomy.

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.

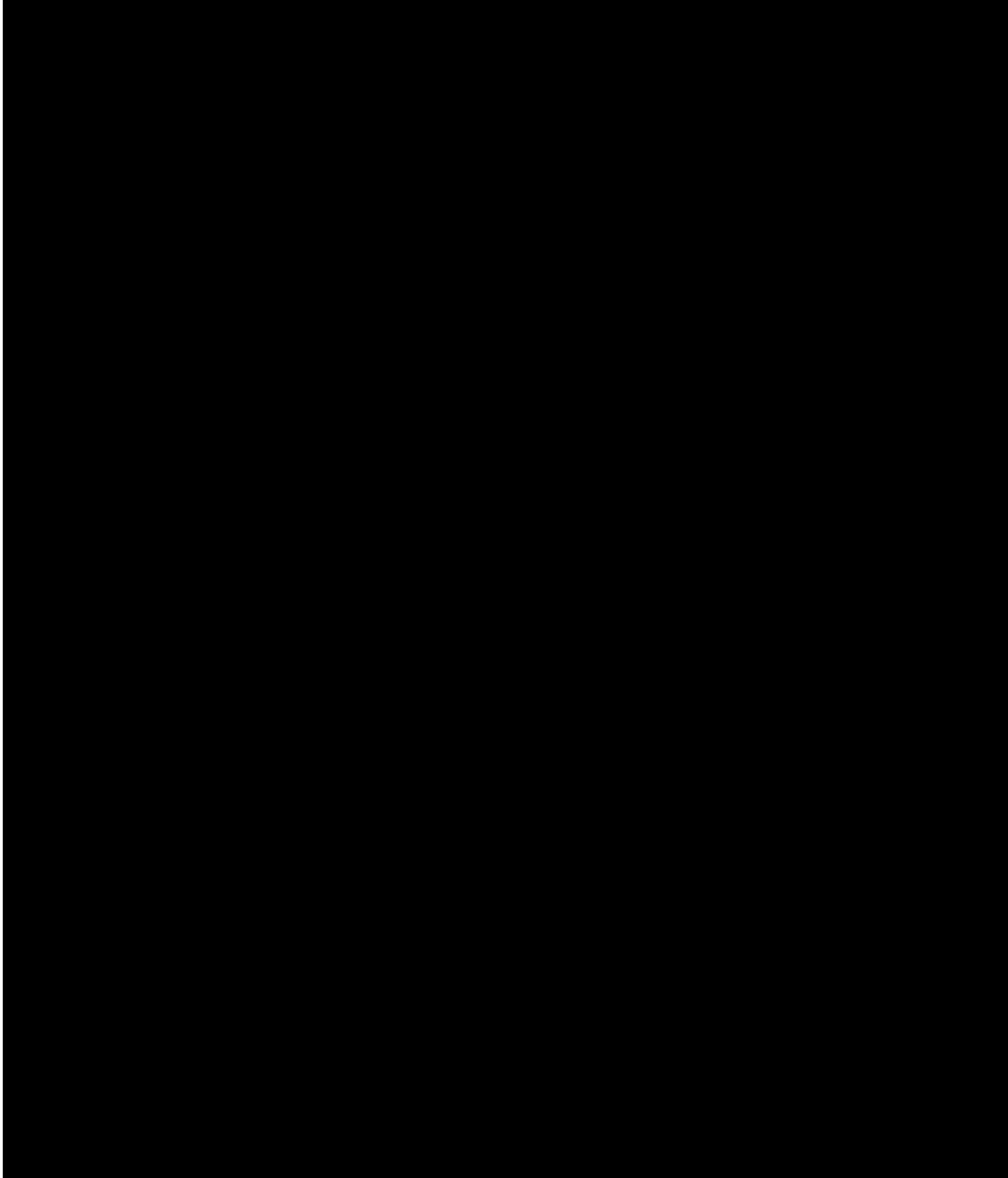
The subject must not take the following disallowed medications at any time during the study, from Screening through the 4-Week Follow-up visit.

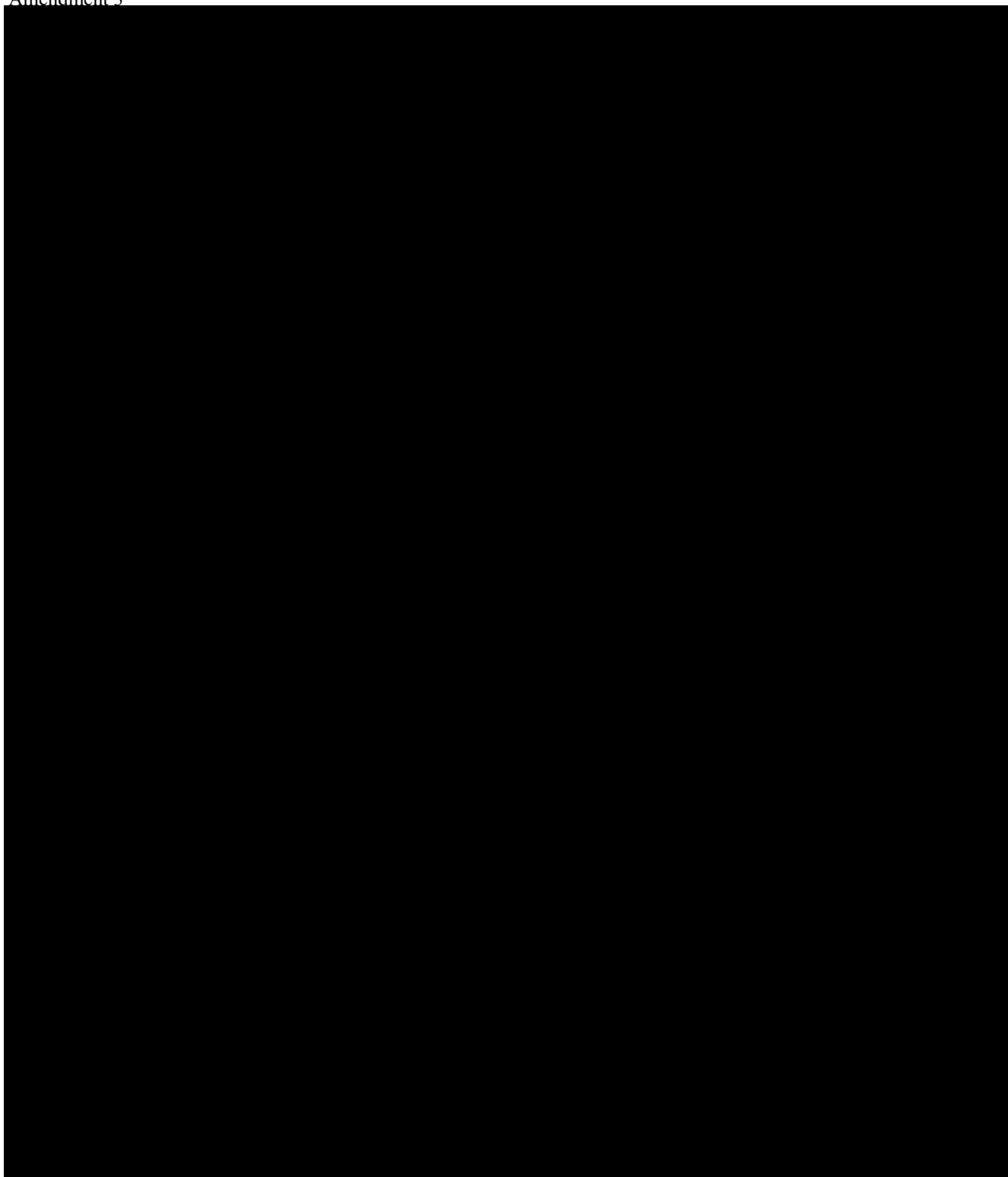
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]







[REDACTED]

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

[REDACTED]

### 20.5 Clinical Laboratory Tests

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

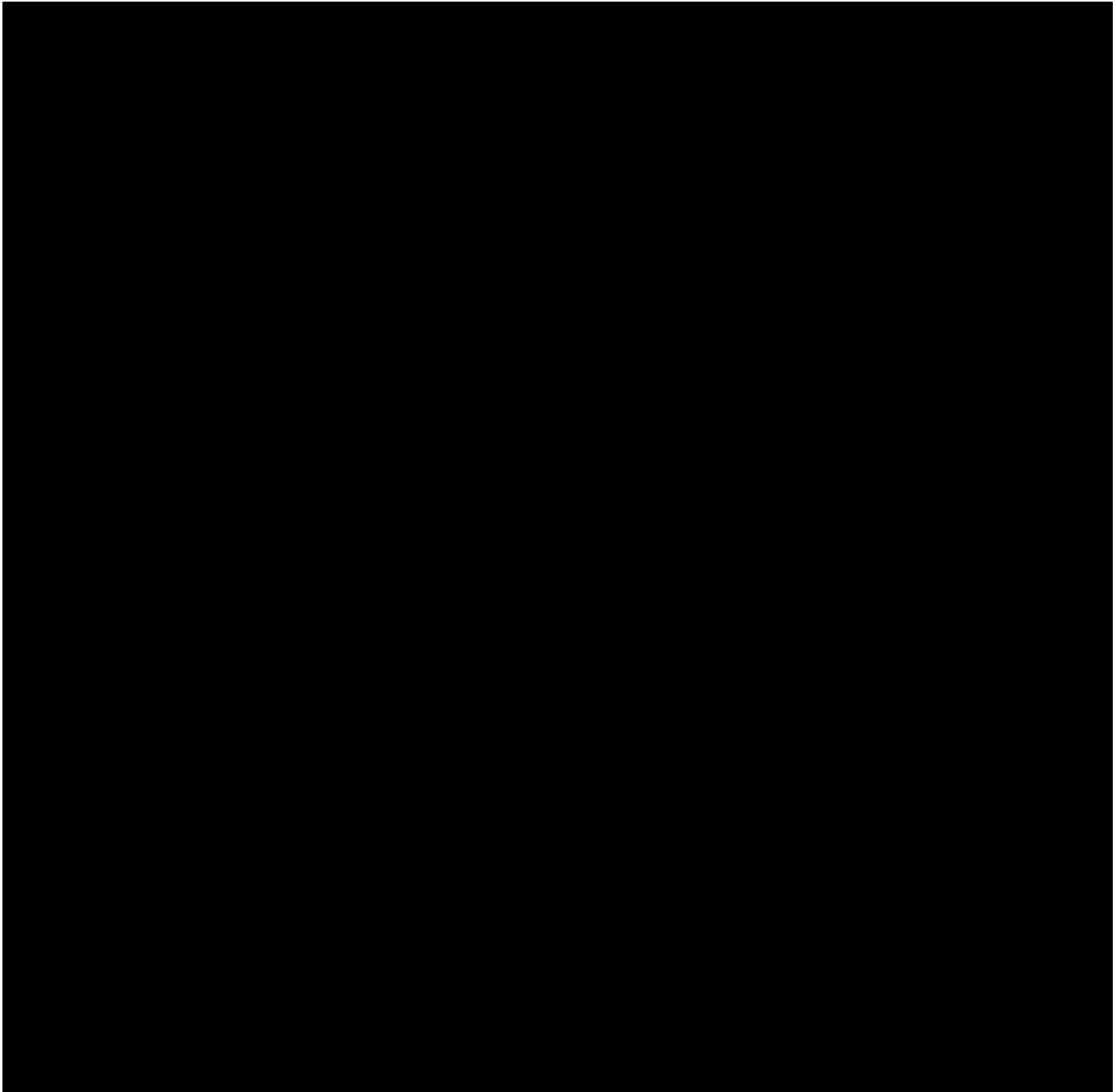
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



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## PROTOCOL AMENDMENT 3 SUMMARY OF CHANGES

### 1. Major changes

- Removal of pre-Baseline visit. Subjects diagnosed with PSC often have elevated but fluctuating liver enzymes (AST, ALT, Total Bilirubin and Direct Bilirubin). Repeating liver enzymes at the pre-Baseline visit, and taking the average value of the Screening and pre-Baseline values for inclusion, has proven prohibitive in subject enrollment due to these normal fluctuations. Subjects with evidence of cirrhosis or hepatic impairment will be excluded by exclusion criterion 9. With the removal of the pre-Baseline visit, the mean values of the AST, ALT, Total Bilirubin and Direct Bilirubin parameters no longer apply, and are revised in exclusion criteria 13 and 14.
- The upper cut-off values of Total Bilirubin and Direct Bilirubin have been changed to:
  - Total Bilirubin > 2.0 mg/dL
  - Direct Bilirubin > 0.8 mg/dL
- Removal of Week 2 visit. Frequent site visits negatively impacts on subjects' willingness to participate in this 6-month study. Therefore, it is decided that monthly visits are sufficient for the first 4 months, then 2 months later at Month 6 (end of treatment period). Based on safety data from other CVC studies, where subjects have been treated for one year, there is no safety impact with the removal of the Week 2 visit.
- Revision of inclusion criterion 3 to allow subjects without inflammatory bowel disease (IBD) to be eligible for the study. There is no impact on safety by allowing patients with or without IBD to participate.
- Revision of inclusion criterion 5 to allow serum ALP  $\geq 1.5 \times$  ULN, rather than only greater than, for study entry.

### 2. Administrative changes

- Updated version date throughout protocol amendment 3.
- [REDACTED]
- Plasma PK samples will not be drawn at Week 2.
- Updated Section 9.3 Prior and Concomitant Therapy medication to allow the use of [REDACTED]
- Updated Section 9.4 Additional Restrictions and Precautions stating results from additional studies indicating that CVC did not demonstrate phototoxic potential in neutral red uptake phototoxicity.

[REDACTED]

- 
- [Redacted]
  - [Redacted]
  - [Redacted]
- [Redacted]
- [Redacted]



## SUMMARY OF CHANGES

**Title:** A Phase 2 Proof of Concept Study Investigating the Preliminary Efficacy and Safety of Cenicriviroc in Adult Subjects with Primary Sclerosing Cholangitis (PSC)

**Protocol Number:** 652-205

**Product:** Cenicriviroc Mesylate (CVC)

**Phase of Study:** Phase 2

**Sponsor:** Tobira Therapeutics, Inc.  
701 Gateway Blvd, Suite 300  
South San Francisco, CA 94080  
United States of America

**Date of Original Protocol:** 19 November 2015  
**Date of Amendment 1.1:** 29 December 2015  
**Date of Amendment 2:** 06 April, 2016

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### Summary of Changes for Protocol 652-205: PERSEUS

The most noteworthy changes for Study 652-205, Amendment 2 are detailed below. All relevant sections have been updated with the appropriate changes including the Schedule of Assessments. In addition, various administrative corrections and edits have been made for clarity. A redline version of the protocol has been provided for comparison from Amendment 1.1 to Amendment 2.0.

- [REDACTED]
- Added clarification that if subjects are deemed eligible (based on their Pre-Baseline results), the Baseline visit can take place immediately or approximately within 2 weeks prior to the Baseline visit
- [REDACTED]
- [REDACTED]
- INR was added for every visit
- Clarified if the subjects do not fast, subjects will need to return to the center in the afternoon (approximately 6 hours later) for his/her fasting blood draw or the visit may be rescheduled within 72 hours
- Added clarification on replacing subjects. If subjects discontinue from the study for reasons other than safety, replacement subjects will be considered.
- The “Special Situations Report” Section has been deleted (Previously in Section 11.4.1.8). This section was inadvertently included in the original protocol. However, for the purpose of this study, reports of medication error, abuse, misuse, or overdose, and reports of adverse reactions associated with product complaints will be reported to Tobira and [REDACTED] for investigation and reporting. Any corrective action items will be followed through with the investigators, as appropriate. Clarified the language referring to guidance if any Grade 4 laboratory abnormalities or clinical events occur.
- Fibrates have been excluded as they may decrease ALP and confound efficacy results
- Clarified IgG total and IgG1 should be performed at Baseline and Week 24
-



## SUMMARY OF CHANGES

**Title:** **A Phase 2 Proof of Concept Study Investigating the Preliminary Efficacy and Safety of Cenicriviroc in Adult Subjects with Primary Sclerosing Cholangitis (PSC)**

**Protocol Number:** **652-205**

**Product:** **Cenicriviroc Mesylate (CVC)**

**Phase of Study:** **Phase 2**

**Sponsor:** **Tobira Therapeutics, Inc.  
701 Gateway Blvd, Suite 300  
South San Francisco, CA 94080  
United States of America**

**Date of Original Protocol:** **19 November 2015**

**Date of Amendment 1.0:** **29 December 2015**






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## Major Changes

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
Section 4 Synopsis (Inclusion Criteria) and Section 8.2 Inclusion Criteria	2. Clinical diagnosis of PSC as evident by chronic cholestasis of more than six months duration with either a consistent magnetic resonance cholangiopancreatography (MRCP)/endoscopic retrograde cholangiopancreatography (ERCP) showing sclerosing cholangitis, or a liver biopsy taken at any time consistent with PSC in the absence of a documented alternative etiology for sclerosing cholangitis.	2. Clinical diagnosis of PSC as evident by chronic cholestasis of more than six months duration with either a consistent magnetic resonance cholangiopancreatography (MRCP)/endoscopic retrograde cholangiopancreatography (ERCP) showing sclerosing cholangitis, or a liver biopsy taken at any time consistent with PSC in the absence of a documented alternative etiology for sclerosing cholangitis. If diagnosis of PSC was made by histology alone, it must require the presence of fibro-obliterative lesions (i.e., onion skin lesions).	Additional sentence “If diagnosis of PSC was made by histology alone, it must require the presence of fibro-obliterative lesions (onion skin lesions)” was added to ensure histological diagnosis included this morphological observation.
Section 4 Synopsis (Inclusion Criteria) and Section 8.2 Inclusion Criteria	3. Confirmed Inflammatory Bowel Disease (IBD)	3. Documented evidence of Inflammatory Bowel Disease (IBD) either by prior endoscopy or in previous medical records, for $\geq 6$ months. In addition, subjects will be required to enter the study with a Partial Mayo Risk score of 0-3, inclusively	Added language to confirm IBD diagnosis, as well as severity of IBD.
Section 4 Synopsis (Exclusion Criteria) and Section 8.3 Exclusion Criteria	13. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $> 5 \times$ ULN	13. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT); above the allowed cut-offs, as determined by the mean Screening and pre-Baseline values (subjects who show evidence of significant worsening of liver transaminases on repeat measure will be excluded): <ul style="list-style-type: none"> <li>• AST <math>&gt; 200</math> IU/L males and females</li> <li>• ALT: males <math>&gt; 250</math> IU/L and females <math>&gt; 200</math> IU/L</li> </ul>	Added detail to ensure that patients do not have deteriorating liver function prior to enrolment

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
Section 4 Synopsis (Exclusion Criteria) and Section 8.3 Exclusion Criteria	14. Bilirubin > 3 × ULN	14. Total Bilirubin and Direct Bilirubin; above the allowed cut-offs, as determined by the mean Screening and pre-Baseline values (subjects who show evidence of significant worsening of bilirubin will be excluded): <ul style="list-style-type: none"> <li>• Total Bilirubin ≥ 1.5 mg/dL</li> <li>• Direct Bilirubin ≥ 0.5 mg/dL</li> </ul>	Added detail to ensure that patients do not have deteriorating liver function prior to enrolment
Figure 7-1 Study Design Schematic	<added a pre-baseline visit in the schematic>	-14d (-2wk)	Added pre baseline visit day in order to ensure that there is no deteriorating liver function on repeat testing prior to enrollment


Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
Section 10.0 Study Procedures	<New paragraphs added>	<p>Eligible subjects will be required to complete a diary daily to assess stool frequency and blood in the stool (Partial Mayo Risk score), daily. In addition, the diary will include a question regarding abdominal pain in order to assess if the subject develops any significant increase in abdominal pain. If a subject exceeds a Partial Mayo Risk score of 4 at any time, by investigator assessment of patient diary as well as subject evaluation, then the subject will be reevaluated for his or her IBD at the clinical research site. Should subjects experience an increase in abdominal pain, stool frequency or blood in their stool between visits, they will be instructed to contact the site immediately for clinical assessment for their IBD.</p> <p>The principal investigator or delegate will be instructed to inquire about abdominal pain at each study visit. As with all adverse events, any abdominal pain will be assessed for severity and causality by the investigator in the eCRF, per Section 11.4.</p>	<p>Added detail on patient diary which will also now include abdominal pain question to assess abdominal pain. The principal investigator will be required to ask about abdominal pain at each visit.</p> <p>In addition, as patients are entering the study with a Partial Mayo Risk score of 0-3, any patient who exceeds a score of 4, will be required to be reevaluated for their IBD.</p>
		 	

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
	<p>■ [REDACTED]</p> <p>■ [REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p>	
<p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>■ [REDACTED]</p> <p>■ [REDACTED]</p> <p>■ [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>S [REDACTED]</p>

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
	<p>[REDACTED]</p>	<p>[REDACTED]</p>	

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
	<p>[REDACTED]</p>	<p>[REDACTED]</p>	





Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
			



## Minor Changes

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
Section 4.0 Synopsis (Study Design)	Screening will occur within 4 weeks before the Baseline Visit (Day 1). At Day -28 (approximately), subjects will undergo all eligibility evaluations per the schedule of assessments.	Screening will occur within 6 weeks before the Baseline Visit (Day 1). At Day -42 (approximately), subjects will undergo all eligibility evaluations per the schedule of assessments. A pre-Baseline visit will occur 2 weeks (Day -14) prior to the Baseline visit for liver parameter testing.	Screening within 4 weeks of Baseline Visit (Day 1) was updated from 4 weeks to 6 weeks and Day -28 was updated to -42 because of inclusion of the pre-Baseline visit, which occurs at week -2 (day -14) in order to get a repeat of liver function parameters prior to enrollment. Additional sentence regarding a pre-Baseline Visit was added as per above.
Section 4 Synopsis (Exclusion Criteria) and Section 8.3 Exclusion Criteria	1. Presence of documented secondary sclerosing cholangitis on prior clinical investigations	1. Presence of documented secondary sclerosing cholangitis (such as ischemic cholangitis, recurrent pancreatitis, intraductal stone disease, severe bacterial cholangitis, surgical or blunt abdominal trauma, recurrent pyogenic cholangitis, choledocholithiasis, toxic sclerosing cholangitis due to chemical agents, or any other cause of secondary sclerosing cholangitis) on prior clinical investigations	Examples of secondary sclerosing cholangitis have been included.
Section 4 Synopsis (Exclusion Criteria) and Section 8.3 Exclusion Criteria	9. History of cirrhosis and/or hepatic decompensation including ascites, encephalopathy or variceal bleeding	9. History of cirrhosis and/or hepatic impairment (Child-Pugh classes A, B and C) and/or hepatic decompensation including ascites, encephalopathy or variceal bleeding. Subjects who show evidence of significant worsening of hepatic function will be excluded	Added the verbiage “impairment (Child-Pugh classes A, B, and C) to clarify no hepatic decompensation or cirrhosis allowed.

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
Section 4 Synopsis (Exclusion Criteria) and Section 8.3 Exclusion Criteria	10. Subjects with fibrosis evidence of cirrhosis, as determined by local transient elastography (TE; e.g., FibroScan®) values of $\geq 13.0$ kPa, taken within the last 6 months. If TE has not been conducted within the 6 months prior to screening then one will be conducted during the screening period and can be used as the Baseline value	10. Subjects with evidence of cirrhosis, as determined by local transient elastography (TE; e.g., FibroScan®) values of $\geq 13.0$ kPa, taken within the last 6 months. If TE has not been conducted within the 6 months prior to screening then one will be conducted during the screening period and can be used as the Baseline value	Removed the word ‘fibrosis’ due to typo in original version (sentence was incorrect and nonsensical).
Section 4 Synopsis (Exclusion Criteria) and Section 8.3 Exclusion Criteria	11. Moderate to Severe active IBD or flare in colitis activity within the last 90 days requiring intensification of therapy beyond Baseline treatment. Subjects with stable mild to moderate IBD, who are on treatment, are allowed provided they are stable for 3 months with 5-amino salicylic acid drugs or Azathioprine	11. Moderate to Severe active IBD or flare in colitis activity within the last 90 days requiring intensification of therapy beyond Baseline treatment. Subjects with stable mild to moderate IBD, who are on treatment, are allowed provided they are stable for 3 months with 5-amino salicylic acid drugs or Azathioprine (allowed dose of azathioprine is 50-200 mg/day).	Added the allowable dose range for azathioprine of 50-200mg/day
Section 4 Synopsis (Exclusion Criteria) and Section 8.3 Exclusion Criteria	15. International normalized ratio $> 1.3$ in the absence of anticoagulants.	15. International normalized ratio (INR) $> 1.3$ in the absence of anticoagulants.	Abbreviation “(INR)” added as it is used elsewhere in the protocol
Section 4 Synopsis (Study Procedures/Frequency)	Screening will occur within 4 weeks before the Baseline Visit.	Screening will occur within 6 weeks before the Baseline Visit. A pre-Baseline visit will occur 2 weeks before Baseline.	Screening within 4 weeks of Baseline Visit (Day 1) was updated to 6 weeks. Additional sentence regarding a pre-Baseline Visit was added to include a -2 week (Day -14) visit in order to get a repeat of liver function parameters prior to enrollment
Section 4 Synopsis (Study Procedures/Frequency)	IgG Total, IgG1 and IgG4 will be collected at Baseline, and Week 24	IgG Total, IgG1 and IgG4 will be collected at Baseline, and Week 24 (IgG4 will also be collected at Screening)	Clarification that IgG4 will also be collected at Screening

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
Section 4 Synopsis (Study Procedures/Frequency)	Transient elastography will be assessed once during the Screening period (between Day -28 to Baseline) and again at Week 24	Transient elastography will be assessed once during the Screening period (between Day -42 to Baseline) and again at Week 24	Changed Day -28 to Day -42 according to new schedule
Section 4 Synopsis (Study Procedures/Frequency)	Plasma pharmacokinetic (PK) samples will be drawn pre-dose at Baseline and at Weeks 2, 12, and 24	Plasma pharmacokinetic (PK) samples will be drawn pre-dose and post-dose at Baseline and at Weeks 2, 12, and 24	Added new post dose sampling
Section 5.4 Clinical Studies with CVC	Overall, 599 subjects have been exposed to CVC, including 440 healthy subjects (of which 8 had mild and 8 had moderate hepatic impairment) and 159 HIV 1 infected subjects) have received at least 1 dose of CVC.	Overall, 599 unique subjects have been exposed to CVC in completed studies, including 440 subjects participating in Phase 1 studies (of which 8 had mild and 8 had moderate hepatic impairment) and 159 HIV-1-infected subjects participating in Phase 2 studies who have received at least 1 dose of CVC.	Updated this section administratively
Section 7.1 Overall Study Design and Plan	Screening will occur within 4 weeks before the Baseline Visit.	Screening will occur within 6 weeks before the Baseline Visit. A pre-Baseline visit for repeat measure of liver parameter tests will occur within 2 weeks before the Baseline visit.	Screening within 4 weeks of Baseline Visit (Day 1) was updated to 6 weeks. Additional sentence regarding a pre-Baseline Visit was added to include a -2 week (Day -14) visit in order to get a repeat of liver function parameters prior to enrollment
Figure 7-1 Study Design Schematic	-28d (-4wk) in the schematic	-42d (-6wk) in the schematic	Screening within 4 weeks of Baseline Visit (Day 1) was updated from 4 weeks to 6 weeks and Day -28 was updated to -42 because to include a -2 week (Day -14) visit in order to get a repeat of liver function parameters prior to enrollment
			

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Section 10.1 Screening	<p>&lt;Screening (Days -28; Visit 1&gt;                      Prior to any clinical procedures and evaluations, written signed informed consent must be obtained. Screening 1 is to occur approximately 4 weeks (28 days) before the Baseline Visit (see Section 10.2).</p>	<p>&lt;Screening (Days -42; Visit 1&gt;                      Prior to any clinical procedures and evaluations, written signed informed consent must be obtained. Screening is to occur approximately 4 weeks (28 days) before the pre-Baseline visit (see Section 10.2), and 6 weeks (42 days) before the Baseline Visit (see Section 10.3).</p>	<p>Screening within 4 weeks of Baseline Visit (Day 1) was updated to 6 weeks. Additional sentence regarding a pre-Baseline Visit was added to include a -2 week (Day -14) visit in order to get a repeat of liver function parameters prior to enrollment</p>
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Section 10.5 4-Week Follow-up	<section title> 4-Week Follow-up (Week 28, Day 196; Visit 9)	<section title> 4-Week Follow-up (Week 28, Day 196; Visit 10)	Additional Pre-Baseline Visit included so Visit number assigned to 4-Week Follow-up is now Visit 10 instead of Visit 9
Section 11.4.2.2 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 CRF. See Section 11.4.1.1.6 for a definition of clinically significant laboratory abnormality.	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 CRF. See Section 11.4.1.1.6 for a definition of clinically significant laboratory abnormality. For management of subjects with elevated liver tests, please refer to Section 11.4.6.4.	Added the last sentence to refer to section 11.4.6.4

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Section	Previous Text (Original Protocol)	Revised Text (Amendment 1.0)	Rationale
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]



<b>Section</b>	<b>Previous Text (Original Protocol)</b>	<b>Revised Text (Amendment 1.0)</b>	<b>Rationale</b>
Section 20.5 Clinical Laboratory Tests	Pre-dose PK Samples (for storage): Baseline and Weeks 12 and 24  PK samples will be stored for analysis and assessment of study drug compliance, if applicable	PK Samples: Baseline and Weeks 2, 12 and 24  PK samples will be collected and stored for analysis. A PK sample must be drawn upon repeat testing for abnormalities of ALP, ALT, AST or total bilirubin	Correction and additional detail for PK samples. Also added that PK samples must be drawn if liver function testing is repeated for abnormalities.

Additional minor editorial changes, clarifications, and corrections are not listed.