Janssen Pharmaceutical K.K.

Clinical Protocol

An open-label study to evaluate the pharmacokinetics (PK) of Darunavir (DRV) and Cobicistat (COBI) after a single-oral administration of Darunavir/Cobicistat Fixed-Dose Combination Tablet in Healthy Japanese Adult Subjects

Protocol TMC114FD1HTX4002; Phase 4

TMC114 + JNJ-48763364-AAA Prezcobix® (Darunavir/Cobicistat)

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

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

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SYNOPSIS

An open-label study to evaluate the pharmacokinetics (PK) of Darunavir (DRV) and Cobicistat (COBI) after a single-oral administration of Darunavir/Cobicistat Fixed-Dose Combination Tablet in Healthy Japanese Adult Subjects

DRV inhibits dimerization of human immunodeficiency virus Type 1 (HIV-1) protease and its enzymatic activity. DRV selectively inhibits cleavage of Gag-Pol polyprotein coded by HIV-1 in the infected cells and thereby suppresses the formation of matured infective viruses. DRV has been shown to have a high affinity to the HIV-1 protease with a *Kd* of 4.5×10^{-12}mol/L and is less likely to be affected by mutations associated with resistance to HIV protease inhibitors.

COBI selectively inhibits CYP3A. COBI is used as a pharmacokinetic enhancer (booster) for drugs which CYP3A-mediated metabolism could reduce bioavailability and shorten elimination half-life. COBI is used in combination with such type drugs to increase the exposure of the drug.

TMC114 + JNJ-48763364-AAA (Prezcobix®) is a combined formulation of two compounds, DRV and COBI, and is intended for treating patients naive to anti-HIV drug treatment and patients without DRV-resistant mutants previously treated with an anti-HIV drug. Normally, one fixed-dose combination tablet is orally administered to adult patients once daily and must be used in combination with other types of anti-HIV drugs.

This study will be conducted as a postmarketing study to evaluate the pharmacokinetics of DRV/COBI after a single oral administration of Prezcobix to healthy Japanese adult subjects.

OBJECTIVES AND HYPOTHESIS

Objectives

Primary Objective

The primary objective is to evaluate the PK of DRV and COBI after a single oral administration of Prezcobix to healthy Japanese adult subjects.

Secondary Objective

The secondary objective is to evaluate the safety after a single oral administration of Prezcobix to healthy Japanese adult subjects

Hypothesis

No formal statistical hypothesis testing is planned for this study. This study is designed to collect PK data in Japanese subjects after a single oral administration of Prezcobix under a fed condition.

OVERVIEW OF STUDY DESIGN

This is a single center open-label, single oral dose study in healthy Japanese adult subjects. The study consists of 3 phases; a screening phase from Day -21 to Day -2, an in-patient phase from Day -1 to Day 4 (dosing day is Day 1), and a follow-up assessment phase scheduled 7 to 10 days after the intake of the study drug or at the time of early withdrawal.

SUBJECT POPULATION

Eight subjects will be enrolled to ensure that at least 6 subjects complete the study up to Day 4. If more than 2 subjects withdraw from the study before completion up to Day 4 for reasons other than safety, additional subjects will be enrolled to ensure that at least 6 subjects complete the study up to Day 4.

Main Criteria for Inclusion

Healthy Japanese men and women between 20 and 55 years of age, inclusive; body mass index (BMI) between 18.0 and 30.0 kg/m^2, inclusive; and body weight not less than 50 kg.

DOSAGE AND ADMINISTRATION

One Prezcobix tablet will be taken in the morning on Day 1. The study drug will be taken orally with 240 mL of noncarbonated water within 30 minutes after start of the standardized breakfast, and the breakfast should be fully ingested within 30 minutes. The study drug must be swallowed whole, not chewed, divided, dissolved or crushed.

PHARMACOKINETIC EVALUATIONS

Venous blood will be collected for the determination of plasma concentrations for each component of DRV/COBI at the following time points;

- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 16, 20, 24, 36, 48, 60, 72 hours postdose and early withdrawal visit

Based on the individual plasma concentration-time data, using the actual sampling times, the following PK parameters will be estimated by noncompartmental analysis. Additional PK parameters may be estimated as well.

PK parameters for DRV and COBI: C_{max}, C_{last}, t_{max}, AUC_{last}, AUC_{∞}, λ_z, $t_{1/2,term}$

SAFETY EVALUATIONS

Safety will be evaluated throughout the study. Following evaluations will be performed according to the TIME AND EVENTS SCHEDULE.

- Adverse Events (AEs)
- Clinical Laboratory Tests
  - – - Hematology Panel
  - – - Biochemistry Panel
  - – - Urinalysis
- 12-lead Electrocardiogram (ECG)
- Vital Signs (blood pressure, pulse, temperature [axillary], respiration rate)
- Physical Examination

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

STATISTICAL METHODS

Sample Size Determination

Eight subjects will be enrolled in the study to ensure that at least 6 subjects complete the study assessments up to Day 4. Based on a previous study, TMC114IFD1003, the maximum observed value of between subject coefficient of variation (CV) for C_{max}, AUC_{last} and AUC_{∞} for DRV and COBI after intake of DRV/COBI as an FDC tablet under fed conditions were 35% for DRV and 44% for COBI in healthy nonJapanese adult subjects. Using an estimate of approximately 40% for between subject CV and a

sample size of 6 subjects, the true mean C_{max}, AUC_{last} and AUC_{∞} for each component of DRV/COBI are estimated to be within 73% to 137% of the observed geometric means with 90% confidence.

Pharmacokinetics

All subjects receiving the study drug and having at least one plasma concentration data after administration will be included in the pharmacokinetic analysis. Plasma concentration data will be tabulated for each component of DRV/COBI. Individual and mean concentration time profiles for each analyte will be visually presented on a linear and logarithmic scale. PK parameters for each analyte will be calculated using data of all the subjects whose concentration-time profiles allow for accurate calculation of PK parameters. The descriptive statistics (eg, number of collected data, mean, standard deviation, median, minimum, maximum, CV and geometric means) of plasma concentrations of each analyte at each time point will be reported. Individual and descriptive statistics of PK parameters of each analyte will be tabulated.

Safety

All subjects who received the study drug will be included in the safety and tolerability analysis. Baseline for all laboratory evaluations, vital signs and ECG will be defined as the last evaluation done before the study drug administration. Safety will be evaluated by examining frequency, severity and type of AEs, and changes in clinical laboratory test values (hematology, biochemistry and urinalysis), physical examination results, vital signs and ECG measurements. Safety data will be summarized using descriptive statistics and frequency tables.

TIME AND EVENTS SCHEDULE

Phase	Screening	In-patient period																					End-of-Study
Study day	Days -21 to -2	Day -1	Day 1															Day 2		Day 3		Day 4	End of Study (Day 7 – 10) or Early Withdrawal
Time			Predose	0 h	0.5 h	1 h	1.5 h	2 h	2.5 h	3 h	4 h	5 h	6 h	9 h	12 h	16 h	20 h	24 h	36 h	48 h	60 h	72 h	
Informed consent (ICF)	X																						
Inclusion/exclusion criteria	X																						
Weight/height	X																						
Medical history and demographics	X																						
Smoking habits	X																						
Urine drug/Breath alcohol test	X	X																					
FSH	X[e]																						
Serum pregnancy test[a]	X[f]																						X[f]
Urine pregnancy test		X[f]																					
Dispense/administer study drug				X																			
Physical examination	X	X	X															X				X	X
Vital signs[a,b]	X	X	X							X								X				X	X
Serology[a, c]	X																						
12-lead ECG[a]	X	X	X							X								X				X	X
Clinical Labs[d]	X	X																X				X	X
Blood sample for PK			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]
Residence in clinic		←																					→
Concomitant medication	throughout the study																						
Adverse events	throughout the study																						

Footnotes:

a. When blood samples are to be collected and 12-lead ECG and/or vital signs are to be checked at the same time point, blood samples will be collected after completion of other evaluations.

b. Vital signs include respiration rate, supine blood pressure, pulse and temperature (axillary) after more than 5 minutes rest.
c. Serology tests include HIV antigen/antibody, hepatitis A virus (HAV) antibody immunoglobulin M (IgM), hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, and serologic test for syphilis.
d. Clinical labs include hematology, biochemistry and urinalysis. Subjects will fast for at least 10 hours prior to the blood sampling for clinical labs.
e. For postmenopausal women only.
f. For women of childbearing potential only.
g. For the early withdrawal visit only.

ABBREVIATIONS

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase
ARV	antiretroviral
AUC_{last}	area under the plasma concentration-time curve from time zero to time the last quantifiable time, calculated by linear trapezoidal summation
AUC_{∞}	area under the plasma concentration-time curve from time zero to infinite time
BMI	body mass index
C_{last}	concentration at last quantifiable time point
C_{max}	maximum plasma concentration
COBI	cobicistat
CRF	case report form
CV	coefficient of variation
CYP	cytochrome P450
DRV	Darunavir
ECG	electrocardiogram
eDC	electronic data capture
FDC	Fixed-dose combination
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IRB	Institutional Review Board
PI	protease inhibitor
PK	pharmacokinetic
PQC	Product Quality Complaint
RBC	red blood cell
rtv	ritonavir
SAE	Serious Adverse Event
$t_{1/2,term}$	terminal elimination half-life
t_{max}	time to reach the maximum plasma concentration
US	United States
WBC	white blood cell
λ_z	elimination rate constant associated with the terminal phase

1. INTRODUCTION

Darunavir (DRV) / cobicistat (COBI) Fixed-Dose Combination Tablet (Prezcobix®) is a fixed dose combination (FDC) tablet containing DRV 800 mg and COBI 150 mg, which enables simplification of the regimen for human immunodeficiency virus (HIV) infection.

For the most comprehensive nonclinical and clinical information regarding Prezcobix, refer to the latest version of the package insert and interview form for Prezcobix

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

DRV is a protease inhibitor (PI) with potent in vitro activity demonstrated against native human immunodeficiency virus (HIV) and multi-resistant clinical isolates. COBI is an investigational pharmacokinetic enhancer of CYP3A substrates without intrinsic antiretroviral (ARV) activity.

1.1. Background

HIV infection and the Acquired Immune Deficiency Syndrome (AIDS) caused by its infection have serious impacts to human and socio-economics. In 2014, it was estimated that there are 36.9 million HIV patients across the world. In 2014, there were 2.0 million patients with new HIV infection globally and 1.6 million deaths. As of 27 December 2015, 17,909 HIV-infected patients and 8,086 AIDS patients were reported in Japan. In 2015, Japan reported 1,006 new HIV infections and 428 new AIDS cases.[2] Introduction of combination antiretroviral therapy (ART) has led to a dramatic reduction in mortality and morbidity in treated HIV-infected individuals. Further improvements in therapy and outcome have been challenged by limitations of the commercially available ARV agents, including safety and tolerability, dosing complexity, and the emergence of viral resistance resulting in reduced ARV activity.

DRV

DRV in combination with low dose ritonavir (rtv), as well as other ARV agents, is currently indicated for the treatment of HIV infection in adult patients.

DRV is a HIV protease inhibitor with potent in vitro activity against wild-type HIV-1. As a result of the drug-screening program aimed at activity against resistant strains of HIV-1, DRV is also active against a large panel of viruses resistant to currently licensed protease inhibitor (PI). DRV has been developed in combination with low-dose rtv which serves as a pharmacokinetic enhancer of DRV.

COBI

COBI is an investigational pharmacokinetic enhancer of CYP3A substrates without intrinsic ARV activity. COBI is a potential substitute for rtv and also has the advantage of being able to be coformulated with DRV resulting in a reduced pill burden and potentially fewer adverse effects. This could result in better adherence to the dosing regimen and therefore less risk in the development of resistance.

DRV/COBI Fixed-Dose Combination Tablet (Prezcobix®)

DRV/COBI FDC (Prezcobix®) tablet is a novel combination tablet containing fixed doses of DRV, a PI and COBI which acts as pharmacoenhancer has been developed in a collaboration research by Janssen Research & Development and Gilead Sciences Inc. One tablet of DRV/COBI combination tablet contains these compounds at the respective recommended dose (DRV 800 mg [ethanol additive as 800 mg of darunavir] and COBI 150 mg (150 mg as cobicistat): this combination tablet must be administered in combination with other ARV drugs.

DRV/COBI FDC (Prezcobix®) has been approved in United States (US) and European Union (EU) countries. In Japan, the DRV/COBI FDC has been approved under the trade name of Prezcobix in November 2016.

Clinical Studies

Prezcobix demonstrated its efficacy and tolerability in phase 3 clinical study (Study GS-US-216-0130) conducted outside Japan involving adult anti-HIV drugs-naïve patients with HIV infections or anti-HIV drug-treated patients with HIV infections without mutations associated with resistance to DRV.

1.2. Overall Rationale for the Study

This study is designed to evaluate the Pharmacokinetic (PK) of DRV/COBI after single oral administration of Prezcobix combination tablet to healthy Japanese adult subjects.

In Japan, the applications for approval for anti-infective drugs for HIV which are approved in foreign country can be submitted without clinical data in Japanese subjects, and their quality, safety and efficacy will be evaluated based on foreign data (ref. “Handling of applications for import or manufacturing approval of anti-infective drugs for HIV” [PMSB / ELD Notification No.1015 dated November 12,1998]). In this case, it is allowed to conduct a study to evaluate PK profiles in Japanese subjects after marketing authorization.

According to this notification, after approval of Prezcobix in US, Janssen Pharmaceutical K.K. submitted the new drug application of Prezcobix only with foreign data, and obtained aproval in Japan in November 2016 with the condition that a clinical single-dose PK study in healthy Japanese subjects will be conducted as a postmarketing study.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

2.1.1. Objectives

Primary Objective

The primary objective is to evaluate the PK of DRV and COBI after a single oral administration of Prezcobix to healthy Japanese adult subjects.

Secondary Objective

The secondary objective is to evaluate the safety after a single oral administration of Prezcobix to healthy Japanese adult subjects.

2.2. Hypothesis

No formal statistical hypothesis testing is planned for this study. This study is designed to collect PK data in Japanese subjects after a single oral administration of Prezcobix under a fed condition.

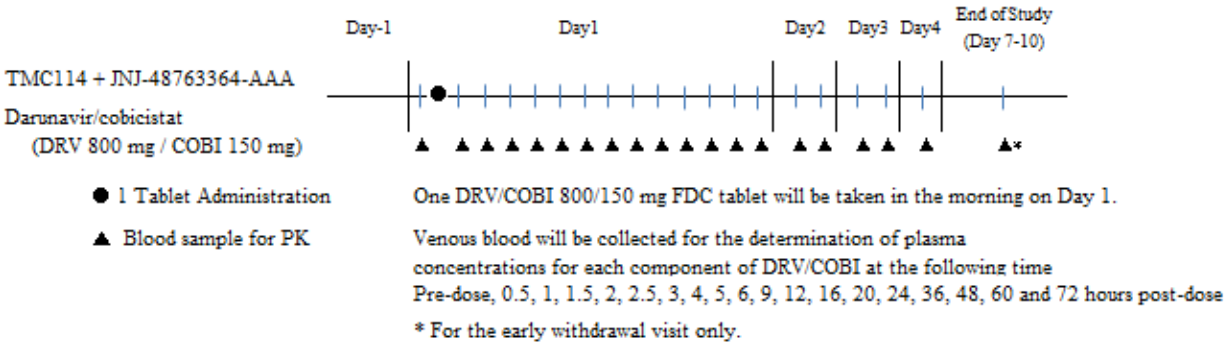
3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a single center open-label, single oral dose study in healthy Japanese adult subjects. Eight subjects will be enrolled to ensure that at least 6 subjects complete the study up to Day 4. The study consists of 3 phases; a screening phase from Day -21 to Day -2, an in-patient period-phase from Day -1 to Day 4 (dosing day is Day 1), and an End of Study phase with a visit scheduled 7 to 10 days after the intake of study drug or at the time of early withdrawal.

As depicted in Figure 1, eight subjects who satisfy all inclusion criteria and do not meet any exclusion criteria will receive Prezcobix at Day 1. Subjects who met the selection criteria at screening will be admitted to the investigational institute on the day before administration (Day -1). All enrolled subjects will receive a single oral dose of one Prezcobix tablet on Day 1 (there is no Day 0) within 30 minutes after start of the standardized breakfast (see Figure 1), and the breakfast should be fully ingested within 30 minutes. All subjects will remain in the investigational institute for the entire duration of the in-patient phase. Subjects will be discharged on Day 4 after the completion of all required assessments. Subjects will visit the investigational institute on the days as scheduled until the last follow-up assessment on Day 7 - Day 10. Serial blood samples for the determination of plasma concentrations for each component of Prezcobix will be collected over a period of 72 hours. Details on the timing of the dose and the PK and safety assessments are given in the TIME AND EVENTS SCHEDULE.

Figure 1: Schedule Overview of the Study



3.2. Study Design Rationale

This open-label, single-arm, single-dose study design is a commonly used design for required postmarketing studies to evaluate PK of anti-HIV drugs in Japan.

This study is designed to evaluate the pharmacokinetics (PK) of DRV and COBI after single dose administration of Prezcobix to healthy Japanese subjects, since there are currently no PK data after administration of Prezcobix to Japanese subjects.

The dose regimen is a single oral dose of Prezcobix taken under a fed condition is selected since this dose is approved for once daily use in Japan and is how it is currently being used in clinical practice.

The frequent blood samplings especially on Day 1 are set to accurately evaluate the PK profiles of each component with different absorption and elimination rates. A t_{max} and $t_{1/2}$ for DRV and COBI in previous study (TMC114IFD1003 in healthy nonJapanese adult subjects) are summarized in Table 1.

Table 1: PK parameter for DRV and COBI in previous study (TMC114IFD1003)

PK parameter	t_{max} : median (min-max), $t_{1/2,term}$: mean (standard deviation)	
	N=40	
	DRV	COBI
t_{max} (h)	4.03 (1.50 - 9.50)	4.00 (1.00 - 5.02)
$t_{1/2,term}$ (h)	6.7 (3.4)	3.8 (0.8)

The blood sampling points in this study are decided as in TMC114IFD1003 study.

Venous blood will be collected for the determination of plasma concentrations for each component of DRV/COBI at the following time points;

Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 16, 20, 24, 36, 48, 60 and 72 hours postdose

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 21 days before administration of the study drug.

Eight subjects will be enrolled to ensure that at least 6 subjects complete the study up to Day 4. If more than 2 subjects withdraw from the study before completion up to Day 4 for reasons other than safety, additional subjects will be enrolled to ensure that at least 6 subjects complete the study up to Day 4.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study.

4.1. Inclusion Criteria

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

1. Subject must be a Japanese man or woman 20 to 55 years of age, inclusive.

2. Subject must be healthy on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. This determination must be recorded in the subject's source documents and initialed by the investigator.

3. Subject must be healthy on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the subject may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study with exception of those parameters listed explicitly in the exclusion criteria. This determination must be recorded in the subject's source documents and initialed by the investigator.

4. Each subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and are willing to participate in the study.

5. A woman of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) at screening and urine pregnancy test at the time of admission to the study site, hospitalization, and must not breast feed from screening onwards.

6. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies.

   Before study drug administration, a woman must be either:

   a. Not of childbearing potential defined as:

      - premenarchal
        A premenarchal state is one in which menarche has not yet occurred.
      - postmenopausal
        A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single follicle stimulating hormone (FSH) measurement is insufficient.
      - permanently sterile
        Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

b. Of childbearing potential and

practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly)
Examples of highly effective contraceptives include
- user-independent methods:
  implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (s*exual abstinence is considered a highly effective method **only** if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.*)
- user-dependent methods:
  combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

If a woman is of childbearing potential, she must agree to remain on a highly effective method throughout the study and for at least 30 days after the last dose of study drug.

7. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of at least 30 days after intake of the study drug.

8. In addition to the user independent highly effective method of contraception, a male or female condom with or without spermicide is required. Male condom and female condom should not be used together (due to risk of failure with friction).

9. During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the dose of study drug, in addition to the highly effective method of contraception, a man.

- who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository).
- who is sexually active with a woman who is pregnant must use a condom must agree not to donate sperm.

10. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

11. Body mass index (BMI; weight [kg]/height^2 [m^2]) between 18 and 30 kg/m^2 (inclusive), and body weight not less than 50 kg.

12. Blood pressure (after the subject is supine for 5 minutes) between 90 and 140 mm Hg systolic, inclusive, and no higher than 90 mm Hg diastolic.

13. Nonsmoker or subject who habitually smokes no more than 10 cigarettes or equivalent of e-cigarettes, or 2 cigars, or 2 pipes of tobacco per day for at least 6 months before study drug administration.

14. Subjects must agree to comply with contraceptive measures as mentioned in Section 4.3 (Prohibitions and Restrictions).

4.2. Exclusion Criteria

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

1. Subject has a history of or current clinically significant medical illness including (but not limited to) cardiac arrhythmias or other cardiac disease, hematologic disease, coagulation disorders (including any abnormal bleeding or blood dyscrasias), lipid abnormalities, significant pulmonary disease, including bronchospastic respiratory disease, diabetes mellitus, liver or renal insufficiency (estimated creatinine clearance below 80 mL/min); thyroid disease, neurologic or psychiatric disease, infection, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, metabolic disturbances or any other illness that the investigator considers should exclude the subject or that could interfere with the interpretation of the study results.

2. Subject has a history of malignancy before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, that is considered cured with minimal risk of recurrence).

3. Subject has a known allergies, hypersensitivity, or intolerance to Prezcobix or its excipients (refer to Package Insert or Interview Form for Prezcobix). [1, 3]

4. Subject has a history of or current clinically significant skin reactions (such as but not limited to Stevens-Johnson Syndrome [SJS], TEN, and/or erythema multiforme) or any history of allergies to drugs, such as, but not limited to, sulfonamides and penicillins.

5. Clinically significant abnormal values for hematology, clinical chemistry, or urinalysis at screening as deemed appropriate by the investigator.

6. Clinically significant abnormal physical examination and vital signs at screening or predose on Day 1, as deemed appropriate by the investigator.

7. The following confirmed laboratory abnormalities at screening as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric AEs and in accordance with the normal ranges of the clinical laboratory:

    a. serum creatinine grade 1 or greater (≥1.1 x upper limit of laboratory normal range [ULN]) or calculated creatinine clearance (CrCL) <80 mL/min; Creatinine clearance (Ccr) is calculated by the Cockcroft-Gault method.
    b. lipase and/or pancreatic amylase grade 1 or greater (≥1.1 x ULN);
    c. hemoglobin grade 1 or greater (≤10.9 g/dL);
    d. platelet count grade 1 or greater (≤124.999 x 10^9/L);
    e. white blood cell (WBC) count grade 1 or greater (≤2.5 x 10^9/L);
    f. absolute neutrophil count grade 1 or greater (≤1.3 x 10^9/L);
    g. aspartate aminotransferase (AST) or alanine aminotransferase (ALT) grade 1 or greater (≥1.25 x ULN);
    h. total bilirubin grade 1 or greater (≥1.1 x ULN);
    i. any other laboratory abnormality of grade 2 or above. For proteinuria (spot urine) ≥2+, and microscopic hematuria (>10 red blood cell [RBC]/high power field), a urine retest should be performed in women after the menstrual period.

    Note: Retesting of abnormal lab values that could lead to exclusion is allowed once. Retesting must take place during an unscheduled visit in the screening phase.

8. Subjects with a past history of heart arrhythmias (extrasystole, tachycardia at rest) or, history of risk factors for Torsade de Pointes syndrome (eg, hypokalemia, family history of long QT syndrome).

    Note: Retesting of abnormal QTcF interval (QTcF > 450msec) value that may lead to exclusion will be allowed once without prior approval from the Sponsor. Retesting will take place during an unscheduled visit in the screening phase. Subjects with a normal value at retest may be included.

9. Subject has been contraindicated DRV and COBI per local prescribing information.

10. Subject has taken any disallowed therapies as noted in Section 8, Prestudy and Concomitant Therapy before the planned first dose of study drug.

11. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 120 days or within a period less than 10 times the drug's half-life, whichever is longer, before the planned dose of study drug or is currently enrolled in an investigational study.

12. Subject is a woman, who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study.

13. Subject is a man who plans to father a child while enrolled in this study or within 3 month after study drug intake.

14. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

15. Preplanned surgery or procedures that would interfere with the conduct of the study.

16. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator .

17. Subject has a history of hepatitis A antibody immunoglobulin M (IgM), hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV or serologic tests for syphilis at Screening.

18. Subject has a history of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at Screening.

19. History of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (4th edition or 5th edition) (DSM-IV or DSM-V) criteria within 5 years before Screening or positive test results for alcohol and/or drugs of abuse (including methadone, barbiturates, opiates, cocaine, cannabinoids, amphetamines and benzodiazepines) at Screening and Day -1.

20. Subject has donated blood or plasma within 60 days preceding the intake of study drug.

21. Subject has previously participated in more than 3 single-dose studies with COBI (GS-9350) and/or DRV (TMC114).

22. Subject has known allergies to heparin or history of heparin induced thrombocytopenia.

23. Subjects with lack of good/reasonable venous access.

24. Subject who is unable to swallow solid, oral dosage forms whole with the aid of water (participants may not chew, divide, dissolve, or crush the study drug).

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from

participation in the study. Section 9.1.2, Screening, describes options for retesting. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8, Prestudy and Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Since the effects of DRV and/or COBI on conception and fetal development are unknown, subject must comply with the contraceptive requirements as indicated in the inclusion criteria.

   For details on the existing data with regard to the reproductive toxicity of DRV, see the current Package Insert or Interview Form.

3. Strenuous exercise may affect study specified assessments and safety laboratory results; for this reason, strenuous exercise should be avoided within 48 hours before all planned study visits and during stays in the investigational institute.

4. Avoid donating blood for at least 90 days after completion (ie, final follow-up visit) of the study.

5. Subjects may not consume food or beverages containing alcohol, grapefruit juice, Seville oranges, or quinine (eg, tonic water) from 24 hours (72 hours in the case of grapefruit juice and Seville oranges) before pharmacokinetic sample collection, until after the last pharmacokinetic sample is collected.

6. Subjects may not consume vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats from 7 days before the intake of study drug until the last pharmacokinetic sample has been taken.

7. If a subject has had a recent febrile illness within 14 days of the scheduled start of study drug intake, the start of study drug intake should be postponed until the body temperature is normal for at least 72 hours.

8. Subjects must refrain from the use of any methylxanthine-containing products, (eg, chocolate bars or beverages, coffee, teas, or colas) from 48 hours before administration of study drug and during confinement, and also must avoid excessive use of caffeine (ie, no more than approximately 500 mg/day, as contained in 5 cups of tea or coffee or 8 cans of cola) for outpatient visits during the entire study (including the screening period).

9. Subjects may not consume food containing poppy seeds during the study.

10. Subjects must consume standard institutional meals during the in-patient period.

11. Throughout the study, prescription or nonprescription medication (including any systemic herbal medications and dietary supplements) other than the study drug are prohibited, except for paracetamol (acetaminophen) or ibuprofen, birth control drugs, hormone replacement therapy, vitamins and the drug for treatment of AEs. See Section 8 for additional information regarding allowed prescription or nonprescription medication.

12. Smoking subjects will not change their stable smoking habits for the duration of the study.

13. Subjects must avoid extreme exposure to the sun or sunbathing, as well as the use of tanning devices (eg, sunbed, solarium) and topical tanning products from screening until the last study-related visit.

14. Subjects must remain at the study site from at least 10 hours before study drug administration until 72 hours postdose blood sampling for PK and safety assessment on Day 4.

5. TREATMENT ALLOCATION AND BLINDING

As this is an open study, blinding procedures are not applicable. No randomization is planned in this study. All the subjects will be assigned to the same treatment.

6. DOSAGE AND ADMINISTRATION

One Prezcobix FDC Tablet, containing 800 mg DRV and 150 mg COBI, will be taken in the morning on Day 1. The study drug will be taken orally with 240 mL of noncarbonated water within 30 minutes after start of the standardized breakfast, and the breakfast should be fully ingested within 30 minutes. The study drug must be swallowed whole, not chewed, divided, dissolved or crushed.

The actual date and time of the study drug administration will be recorded in the case report form (CRF).

As a rule, subjects are to remain in an upright position from the time of the study drug administration until 4 hours after the study drug administration.

The actual start and end time and date of the breakfast on Day 1 will be recorded in the CRF. The start time and date of lunch will also be recorded in the CRF.

Standardized breakfast:

Standardized breakfast (21 g fat, 533 kcal) will be served consisting of (or its equivalent) 4 slices of bread, 2 slices of ham and/or cheese, butter, jelly, and 2 cups (up to 480 mL) of decaffeinated coffee or tea with milk and/or sugar, if desired.

Details of DOSAGE AND ADMINISTRATION were shown on the following Table 2.

Table 2: Description of Interventions

Treatment name	TMC114 + JNJ-48763364-AAA
Test articles(s)	Prezcobix, DRV/COBI
Description	FILM-COATED TABLET
Dose per delivery	1 tablet (DRV 800 mg/COBI 150 mg)
Frequency	1 time on Day 1
Total daily dose	DRV 800 mg/ COBI 150 mg
Delivery method	oral administration during or immediately after a meal

7. TREATMENT COMPLIANCE

Study drug will be administered in the controlled environment of the investigational institute and the direct observation of the administration of the study drug by investigators or investigational staff will ensure compliance with study requirements.

8. PRESTUDY AND CONCOMITANT THERAPY

All medication including over-the-counter medication, must have been discontinued at least 14 days before the intake of study drug (Day 1), except for paracetamol (acetaminophen) or ibuprofen, birth control drugs, hormone replacement therapy, and vitamins. Subjects must not use any medication other than the study drug up to 7 days after the intake of study drug, except for paracetamol (acetaminophen) or ibuprofen, birth control drugs, hormone replacement therapy, and vitamins. Subjects must also not use any systemic herbal medications or dietary supplements including products containing Hypericum perforatum (eg, St. John's Wort) from 28 days before the intake of study drug and up to 7 days after the intake of study drug.

Paracetamol (acetaminophen) or ibuprofen may be used up to 3 days before the intake of study drug. After that, the clinical investigator may permit the use of paracetamol (acetoaminophen) or ibuprofen from 3 days before the intake of study drug until the day of study drug intake, at no more than 500 mg per dose and no more than 1,500 mg per day for paracetamol (acetaminophen), or at no more than 200 mg per dose and no more than 600 mg per day for ibuprofen. In case paracetamol (acetaminophen) or ibuprofen is used, the dose and dosage regimen as well as the indication for use must be recorded in the Concomitant Therapy section of the eCRF.

Female subjects of childbearing potential must use birth-control methods as outlined above in Section 4 and must be willing to continue practicing these birth-control methods throughout the study and for at least 30 days after the intake of study drug. The use of hormonal contraceptives should be recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts should be respected.

Hormone replacement therapy is allowed in postmenopausal women. The use of hormone replacement therapy should be recorded in the Concomitant Therapy section of the eCRF. Applicable procedures and treatment guidance based on package inserts should be respected.

All medications taken by a subject (prescription or nonprescription) that are not the study drug must be documented in the concomitant therapy section of the CRF. This includes medications taken during the period from the screening to the study drug administration.

Other concomitant medication is allowed in the following cases:

- In case of cutaneous reaction/rash and/or an allergic reaction, the use of (levo) cetirizine, topical corticosteroids, topical vitamin A and D ointment, or antipruritic agents in the recommended dosing scheme is permitted.
- In case of nausea (grade 1 and 2), the use of antiemetics (domperidone and metoclopramide) will be permitted.
- In case of diarrhea (grade 1 and 2), the use of loperamide will be allowed.
- Drugs for treatment of AEs

In case any of these medications or vitamins is used, the dose and dosage regimen must be recorded in the Concomitant Therapy section of the eCRF.

If a subject requires use of a disallowed medication, a request for such use must be reviewed by the Sponsor and if approved, subjects may continue to participate in the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

See TIME AND EVENTS SCHEDULE for details

9.1. Study Procedures

9.1.1. Overview

The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of PK, and safety measurements applicable to this study.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: Vital signs and ECG assessments must be done before blood collection. Actual dates and times of assessments will be recorded in the source documentation and CRF.

The total blood volume for the study is approximately 147 mL. Details were shown on the following Table 3.

Table 3: Volume of Blood to be Collected from Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and posttreatment assessments)			
-Hematology	8 mL	5	40 mL
-Serum chemistry	2 mL	5	10 mL
Serology (HIV, hepatitis, syphilis)	6 mL	1	6 mL
Serum β-hCG pregnancy tests[b]	2 mL	2	4 mL
FSH test[c]	2 mL	1	2 mL
Pharmacokinetic samples	3 mL	19	57 mL
Loss by use of indwelling intravenous cannula	2 mL	14	28 mL
Approximate Total[d]			147 mL

a. Calculated as number of samples multiplied by amount of blood per sample.
b. For women of childbearing potential only
c. For postmenopausal women only
d. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
Note: An indwelling intravenous cannula may be used for blood sample collection.

For each subject, the maximum amount of blood drawn from each subject in this study will not exceed 147 mL.

The total blood volume to be collected from each subject will be approximately 147 mL.

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

If blood samples are collected via an indwelling cannula, an appropriate amount (ie, 2 mL) of fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 10 U/mL of sodium heparin and filled to the volume equal to the dead space volume of the lock.

9.1.2. Screening

At the screening visit, after the signing of the ICF, a physical examination will be conducted. Concomitant medication will be recorded. The subject's characteristics (height, weight), smoking habits, and demographic data will be recorded. The overall eligibility of the subject to participate in the study will be assessed.

At the screening visit, the results of the laboratory tests must be within the limits specified in exclusion criteria 7. Exceptional and limited retesting of abnormal screening values that lead to exclusion are allowed only once using an unscheduled visit during the screening period (to reassess eligibility). The investigator may consider the subject eligible if the previously abnormal laboratory test result is within normal range on a repeat testing in the laboratory. At the screening visit, serology tests are including HIV antigen/antibody, hepatitis A virus (HAV) antibody IgM, HBsAg, HCV antibody, and serologic test for syphilis, a breath alcohol test and a urine drug screening will be performed. A serum pregnancy test will be performed for women of

childbearing potential only. A FSH test will be performed for postmenopausal women only. A blood sample for serology, hematology and biochemistry and a urine sample for urinalysis will be taken. Vital signs and a 12-read ECG will be recorded.

9.1.3. In-patient period

Day -1

At Day -1, a physical examination will be conducted, a breath alcohol test, and a urine drug screening will be performed. A urine pregnancy test will be performed only for women of childbearing potential. A blood sample for hematology and biochemistry, and a urine sample for urinalysis will be taken. Vital signs and a 12-read ECG will be recorded.

Day 1

At Day 1, all subjects participating in the study will receive single-dose of one Prezcobix combination tablet, and a physical examination will be conducted predose. At the same time, vital signs and a 12-read ECG will be recorded.

Day 1 - Day 4

The frequency and timing of the PK and safety assessments during the in-patient period are detailed in the TIME AND EVENTS SCHEDULE.

Day 2 and Day 4

At Day 2 and Day 4, a physical examination will be conducted on 24h and 72h after administration. At the same time, a blood sample for hematology and biochemistry and a urine sample for urinalysis will be taken, and vital signs and a 12-read ECG will be recorded.

Subjects will be discharged on Day 4 after the completion of all required assessments.

9.1.4. End of Study

At the end of study or early withdrawal, a physical examination will be conducted. A serum pregnancy test will be performed for women of childbearing potential only. A blood sample for hematology and biochemistry and a urine sample for urinalysis will be taken. Sample PK will be performed for early withdrawal visit only. Vital signs and a 12-read ECG will be recorded.

9.2. Efficacy Evaluations

This item is not applicable in this study.

9.3. Initial Subject Characteristics

Following information will be collected.

- Date of visit (dd/MMM/yyyy)
- Date of birth (dd/MMM/yyyy)
- Date of informed consent (dd/MMM/yyyy)

- Race
- Sex
- Weight and height

9.4. Pharmacokinetics

Following information will be collected.

9.4.1. Evaluations

Venous blood samples of approximately 3 mL will be collected for measurement of plasma DRV/COBI concentrations at the time points indicated in the TIME AND EVENTS SCHEDULE.

Venous blood samples will be collected and each plasma sample will be divided into 2 aliquots (1 for PK and 1 for back-up). Samples collected for analyses of plasma DRV/COBI concentration may additionally be used to evaluate safety aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained. At visits where plasma DRV/COBI concentration will be evaluated, 1 blood draw of sufficient volume can be used. Refer to the separate PK lab manual for further information regarding handling and shipment of plasma samples.

9.4.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of DRV and COBI using a validated, specific, and sensitive LC-MS/MS method by or under the supervision of the sponsor.

9.4.3. Pharmacokinetic Parameters

Based on the individual plasma concentration-time data, using the actual sampling times, the following PK parameters will be derived from the bioanalytical results and will be estimated by noncompartmental analysis. Additional PK parameters may be estimated as well.

- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 16, 20, 24, 36, 48, 60, 72 hours postdose and early withdrawal visit

PK parameters to be estimated from each plasma DRV/COBI concentration-time profiles include, but not limited to:

- C_{max} - maximum plasma concentration
- C_{last} - concentration at last quantifiable time point
- t_{max} - time to reach the maximum plasma concentration
- AUC_{last} - area under the plasma concentration-time curve from time zero to time the last quantifiable time, calculated by linear trapezoidal summation
- AUC_{∞} - area under the plasma concentration-time curve from time zero to infinite time

- λ_z - elimination rate constant associated with the terminal phase
- $t_{1/2,term}$ - terminal elimination half-life

9.5. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event (AE) section of the CRF.

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

The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE:

AEs

AEs will be reported by the subject for the duration of the study. AEs will be followed by the investigator as specified in Section 12, AE Reporting.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology and urine samples for urinalysis will be collected for evaluation of laboratory safety parameters. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE Section of the CRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the investigational institute:

- Hematology Panel

-hemoglobin
-hematocrit
-RBC count
-RBC parameters:
*mean corpuscular hemoglobin (MCH)
*MCH concentration (MCHC)
*mean corpuscular volume (MCV)
-white blood cell (WBC) count with differential
*neutrophils (fraction, %)
*lymphocytes (fraction, %)
*monocytes (fraction, %)
*eosinophils (fraction, %)
*basophils (fraction, %)
-platelet count

*Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory.
In addition, any other abnormal cells in a blood smear will also be reported.

- Serum Chemistry Panel

-sodium
-potassium
-chloride
-blood urea nitrogen (BUN)
-creatinine
-alkaline phosphatase (ALP)
-creatinine phosphokinase (CPK)
-lactic acid dehydrogenase (LDH)
-uric acid
-calcium (corrected for albumin)

-glucose	-phosphate
-aspartate aminotransferase (AST)	-serum albumin
-alanine aminotransferase (ALT)	-total protein
-gamma-glutamyltransferase (GGT)	-total cholesterol
-total bilirubin	-high-density lipoprotein (HDL) cholesterol
-direct bilirubin	-low-density lipoprotein (LDL) cholesterol
-indirect bilirubin	-triglycerides
-calculated CrCl*	-magnesium

*Creatinine clearance (Ccr) is calculated by the Cockcroft-Gault method. The calculated ClCr value is multiplied by 0.85 if female.
Ccr = (140 - age) × body weight (kg) / (72 × creatinine) × 0.85 (if female)

- Urinalysis

Dipstick	Sediment
-glucose	-RBC
-protein	-WBC
-blood	-squamous epithelial cells
-pH	
-ketones	Specific gravity

- At screening and at end of the study, a serum pregnancy test will be performed for women of childbearing potential only.
- On Day -1, urine Pregnancy Testing for women of childbearing potential only.
- At screening, a FSH test will be performed for postmenopausal women only.
- At screening, Serology (HIV antigen/antibody, hepatitis A antibody IgM, hepatitis B surface antigen, and hepatitis C virus antibody) and serologic test for syphilis.
- At screening and on Day -1, urine Drug Screen (methadone, barbiturates, amphetamines, benzodiazepines, cocaine, cannabinoids, and opioids).
- At screening and on Day -1, a Breath Alcohol Testing will be performed.

Presence of changes

If the value meets any of the following, it will be assessed as “change present”:

- The baseline value is within the normal range and the postdose value shows a deviation from the normal range.
- Both baseline and postdose values show deviations from the normal range and the change show a worsening trend.
- Both baseline and postdose values are within the normal range; however the change requires monitoring.

Handling of laboratory data assessed as “change present”

If laboratory value after study treatment is assessed as “change present”, the evaluation will be conducted in accordance with any one of the following criteria:

- If the change is considered clinically insignificant because it is within physiologic changes or it is a change characteristic of the subject, the change will be judged as "physiologic change".

- If the change is considered clinically significant, it will be judged as an abnormal change and recorded in the column of AEs in the CRF.

- If the reason of the abnormal clinical laboratory test value is obviously not related to the subject, the reason (eg, worsening of sample storage conditions or hemolysis) will be recorded.

Electrocardiogram (ECG)

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

Clinically relevant abnormalities occurring during the study should be recorded in the AE section of the eCRF.

Vital Signs (temperature, pulse/heart rate, respiratory rate, blood pressure)

Blood pressure and pulse/heart rate measurements will be assessed in supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

Presence of changes

If the value meets any of the following, it will be assessed as "change present":

- The baseline value is within the normal range and the postdose value shows a deviation from the normal range.
- Both baseline and postdose values show deviations from the normal range and the change show a worsening trend.
- Both baseline and postdose values are within the normal range; however the change requires monitoring.

Handling of vital signs data assessed as "change present"

If vital sign value after study treatment is assessed as "change present", the evaluation will be conducted in accordance with any one of the following criteria:

- If the change is considered clinically insignificant because it is within physiologic changes or it is a change characteristic of the subject, the change will be judged as "clinically insignificant physiologic change" and no abnormality will be recorded as AE.
- If the change is considered clinically significant, it will be judged as an abnormal change and recorded in the column of AEs in the CRF.

Physical Examination

Physical examinations will be conducted at times indicated in the TIME AND EVENTS SCHEDULE.

Any clinically significant abnormalities persisting at the end of the study will be followed by the investigators until resolution or reaching a clinically stable endpoint.

9.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. If blood samples are collected via an indwelling cannula, an appropriate amount (ie, 2 mL) of fluid slightly greater than the dead space volume of the lock will be removed from the cannula and discarded before each blood sample is taken. After blood sample collection, the cannula will be flushed with 10 U/mL of sodium heparin and filled to the volume equal to the dead space volume of the lock.

Refer to the TIME AND EVENTS SCHEDULE for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in Method for Pharmacokinetics Sample Collection, Handling and Shipping (PK) that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in Method for Pharmacokinetics Sample Collection, Handling and Shipping (PK).

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed all the required assessments.

10.2. Withdrawal From the Study

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

- subjects who vomit within 6 hours after study drug administration
- Lost to follow-up
- Withdrawal of consent

- Death
- Noncompliance defined as :
  - subject is not in compliance with requirements of the study, including inclusion criteria, exclusion criteria, and prohibitions and restrictions

If a subject withdraws from the study for any reason before the end of the study, end-of-treatment assessments should be obtained.

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

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. If a subject withdraws from the study before the end of the study, end-of-treatment assessments should be obtained.

If more than 2 subjects withdraw before the completion of all the assessments scheduled on Day 4 for reason other than safety, additional subjects will be enrolled to ensure at least 6 subjects complete all the assessments scheduled on Day 4.

11. STATISTICAL METHODS

No formal hypothesis testing will be conducted. Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

11.1. Subject Information

For all subjects who receive at least one dose of study drug descriptive statistics will be provided. All demographic (eg, age, height, weight, BMI) and other initial subject characteristics (eg, medical history, physical examination) will be tabulated and analyzed descriptively.

11.2. Sample Size Determination

Eight subjects will be enrolled in the study to ensure that at least 6 subjects complete the study assessments up to Day 4. Based on a previous study, TMC114IFD1003, the maximum observed value of between subject coefficient of variation (CV) for C_{max}, AUC_{last} and AUC_{∞} for DRV and COBI after intake of DRV/COBI as an FDC tablet under fed conditions were 35% for DRV and 44 % for COBI in healthy nonJapanese adult subjects. Using an estimate of approximately 40% for between subject CV and a sample size of 6 subjects, the true mean C_{max}, AUC_{last} and AUC_{∞} for each component of DRV/COBI are estimated to be within 73% to 137% of the observed geometric means with 90% confidence.

11.3. Pharmacokinetic Analyses

All subjects receiving the study drug and having at least one plasma concentration data after administration will be included in the pharmacokinetic analysis. Plasma concentration data will be tabulated for each component of DRV/COBI. Individual and mean plasma DRV/COBI concentration and concentration time profiles for each analyte will be visually presented on a linear and logarithmic scale. PK parameters for each analyte will be calculated using the data of all the subjects whose concentration-time profiles allow accurate calculation of PK parameters.

The descriptive statistics (eg, number of collected data, mean, standard deviation, median, minimum, maximum, CV, geometric means and 90% confidence intervals) of plasma concentrations of each analyte at each time point will be reported. Individual and descriptive statistics of PK parameters of each analyte will be tabulated.

PK parameters will be estimated using a noncompartmental analysis method with Phoenix WinNonlin® (Version 6.4).

11.4. Safety Analyses

All subjects who received the study drug will be included in the safety and tolerability analysis. Baseline for all laboratory evaluations and vital signs will be defined as the last evaluation done before the first study drug administration. Safety will be evaluated by examining frequency, severity and type of AEs, and changes in clinical laboratory test values, physical examination results, vital signs and ECG measurements.

AEs

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

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

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Normal ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results will be presented in preversus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Electrocardiogram (ECG)

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

Vital Signs

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

The percentage of subjects with values beyond clinically important limits will be summarized.

Physical Examination

Physical examination findings and changes from baseline will be summarized at each scheduled time point.

12. ADVERSE EVENT REPORTING

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

12.1. Definitions

12.1.1. AE Definitions and Classifications

AE

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

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

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

SAE

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

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

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

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

Unlisted (Unexpected) AE/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Prezcobix, the expectedness of an AE will be determined by whether or not it is listed in the Package Insert.

AE Associated With the Use of the Drug

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

12.1.2. Attribution Definitions

Not Related

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

Doubtful

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

Possible

An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

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

12.3. Procedures

12.3.1. All Adverse Events

All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. SAEs, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSAR). For anticipated events reported as individual SAEs the sponsor will make a determination of relatedness in addition to and independent of the investigator’s assessment. The sponsor will periodically evaluate the accumulating data and, when there is sufficient evidence and the sponsor has determined there is a reasonable possibility that the drug caused a serious anticipated event, they will submit a safety report in narrative format to the investigators (and the head of the investigational institute where required). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

The subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Name of the site

- Site number
- Subject number

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in a study within 30 days of the dose of study drug, whether or not the event is expected or associated with the study drug, is considered an SAE.

12.3.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using

the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

The Prezcobix supplied for this study is a FDC tablet that contains 800 mg of DRV and 150 mg of COBI. It will be manufactured and provided under the responsibility of the sponsor. Refer to the Package Insert for a list of excipients.

14.2. Packaging

Study drug will be packaged in bulk bottle which contains 30 tablets.

14.3. Labeling

Study drug labels will contain information which meets the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject must be documented on the drug accountability form.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study drug will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Package Insert for Prezcobix
- Interview Form for Prezcobix
- Pharmacy manual/study site investigational product and procedures manual
- Laboratory manual

- eDC Manual
- Sample ICF
- Contact information page(s)

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected (147 mL) is considered to be within the normal range allowed for healthy adults over the study time frame according to the Japanese blood donation rule.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

GCPis an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Package Insert for Prezcobix
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved. Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

When prior consent of the subject is not possible, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject must be informed about the study as soon as possible and give consent to continue.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be

put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for nonacceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All

reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject did not participate into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

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

At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The investigator and sponsor will discuss and agree on the source documentation before the receiving consent from the first subject.

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

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

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory to the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided with study-site personnel before the start of the study.

The sponsor will review CRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an

agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study site will be closed upon study completion. A

study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding Prezcobix or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of Prezcobix, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain CRF data from all study sites that participated in the study and direct transmission of clinical laboratory data from a local laboratory into the sponsor's database. Recruitment

performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

REFERENCES

1. Interview Form for Prezcobix®, Edition 1, November 2016
2. Journal of health and welfare statistics. 2016/2017; 63 (9), suppl
3. Package Insert for Prezcobix®, Edition 1, November 2016

Attachment 1: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (version 2.0, November 2014), or 'DAIDS grading table', is a descriptive terminology to be utilized for adverse event reporting in this study. A grading (severity) scale is provided for each adverse event term.

General Instructions

Estimating Severity Grade

If the need arises to grade a clinical adverse event that is not identified in the DAIDS grading table, use the category 'Estimating Severity Grade' located at the top of the table on the following page. In addition, all deaths related to an adverse event are to be classified as grade 5.

Grading Adult and Pediatric Adverse Events

The DAIDS grading table includes parameters for grading both adult and pediatric adverse events. When a single set of parameters is not appropriate for grading specific types of adverse events for both adult and pediatric populations, separate sets of parameters for adult and/or pediatric populations (with specified respective age ranges) are provided. If there is no distinction in the table between adult and pediatric values for a type of adverse event, then the single set of parameters listed is to be used for grading the severity of both adult and pediatric events of that type.

Determining Severity Grade

If the severity of an adverse event could fall under either 1 of 2 grades (eg, the severity of an adverse event could be either grade 2 or grade 3), select the higher of the 2 grades for the adverse event.

Laboratory normal ranges should be taken into consideration to assign gradings to a laboratory value.

Definitions

Basic self-care functions	Adults: activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding Young children: activities that are age and culturally appropriate (eg, feeding self with culturally appropriate eating implements)
Usual social & functional activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults: adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby Young Children: activities that are age and culturally appropriate (eg, social interactions, play activities, learning tasks)
Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.

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

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

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

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

[2] As per Bazett's formula.

DERMATOLOGIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (eg, oral antibiotics, antifungals, antivirals)	IV treatment indicated (eg, IV antibiotics, antifungals, antivirals)	Life-threatening consequences (eg, sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable* For the rash management applicable in this study, see Section 9.3.	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

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

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

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

GASTROINTESTINAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (eg, diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea *≥1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
<1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (eg, liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (eg, hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (eg, aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (<24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for >48 hours OR Rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (eg, circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)

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

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

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

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

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

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

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

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

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

SYSTEMIC				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[9]	Mild signs and symptoms AND Therapy (ie, antibody infusion) interruption not indicated	Therapy (ie, antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (eg, requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to <38.6°C or 100.4 to <101.5°F	≥38.6 to <39.3°C or ≥101.5 to <102.7°F	≥39.3 to <40.0°C or ≥102.7 to <104.0°F	≥40.0°C or ≥104.0°F
Pain[10] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[11]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (eg, antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (eg, steroids or IV fluids)	Life-threatening consequences (eg, requiring pressor or ventilator support)
Underweight[12] *>5 to 19 years of age*	NA	WHO BMI z-score <-2 to ≤-3	WHO BMI z-score <-3	WHO BMI z-score <-3 with life-threatening consequences
2 to 5 years of age	NA	WHO Weight-for-height z-score <-2 to ≤-3	WHO Weight-for-height z-score <-3	WHO Weight-for-height z-score <-3 with life-threatening consequences
<2 years of age	NA	WHO Weight-for-length z-score <-2 to ≤-3	WHO Weight-for-length z-score <-3	WHO Weight-for-length z-score <-3 with life-threatening consequences

[9] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[10] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section.
[11] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[12] WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants >5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤5 years of age.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Weight Loss (excludes postpartum weight loss)	NA	5 to <9% loss in body weight from baseline	≥9 to <20% loss in body weight from baseline	≥20% loss in body weight from baseline OR Aggressive intervention indicated (eg, tube feeding, total parenteral nutrition)

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

SITE REACTIONS TO INJECTIONS AND INFUSIONS				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[13] *Report only one* *>15 years of age*	2.5 to <5 cm in diameter OR 6.25 to <25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥5 to <10 cm in diameter OR ≥25 to <100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥10 cm in diameter OR ≥100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤15 years of age	≤2.5 cm in diameter	>2.5 cm in diameter with <50% surface area of the extremity segment involved (eg, upper arm or thigh)	≥50% surface area of the extremity segment involved (eg, upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*	Same as for **Injection Site Erythema or Redness,** *>15 years of age*
≤15 years of age	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[13] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

LABORATORY VALUES				
CHEMISTRIES				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Acidosis	NA	pH ≥7.3 to <LLN	pH <7.3 without life-threatening consequences	pH <7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to <LLN *30 to <LLN*	≥2.0 to <3.0 *≥20 to <30*	<2.0 *<20*	NA
Alkaline Phosphatase, High	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Alkalosis	NA	pH > ULN to ≤7.5	pH >7.5 without life-threatening consequences	pH >7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to <1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to <2.5 x ULN	2.5 to <5.0 x ULN	5.0 to <10.0 x ULN	≥10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to <LLN *16.0 to <LLN*	11.0 to <16.0 *11.0 to <16.0*	8.0 to <11.0 *8.0 to <11.0*	<8.0 *<8.0*
Bilirubin ***Direct Bilirubin[14], High*** *>28 days of age* *≤28 days of age* ***Total Bilirubin, High*** *>28 days of age* *≤28 days of age*	 NA ULN to ≤1 mg/dL 1.1 to <1.6 x ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates	 NA >1 to ≤1.5 mg/dL 1.6 to <2.6 x ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates	 >ULN >1.5 to ≤2 mg/dL 2.6 to < 5.0 x ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates	 >ULN with life-threatening consequences (eg, signs and symptoms of liver failure) >2 mg/dL ≥5.0 x ULN See Appendix A. Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) *≥7 days of age* *<7 days of age*	10.6 to <11.5 *2.65 to <2.88* 11.5 to <12.4 *2.88 to <3.10*	11.5 to <12.5 *2.88 to <3.13* 12.4 to <12.9 *3.10 to <3.23*	12.5 to <13.5 *3.13 to <3.38* 12.9 to <13.5 *3.23 to <3.38*	≥13.5 *≥3.38* ≥13.5 *≥3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	>ULN to <6.0 *>ULN to <1.5*	6.0 to <6.4 *1.5 to <1.6*	6.4 to <7.2 *1.6 to <1.8*	≥7.2 *≥1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥7 days of age* *<7 days of age*	7.8 to <8.4 *1.95 to <2.10* 6.5 to <7.5 *1.63 to <1.88*	7.0 to <7.8 *1.75 to <1.95* 6.0 to <6.5 *1.50 to <1.63*	6.1 to <7.0 *1.53 to <1.75* 5.50 to <6.0 *1.38 to <1.50*	<6.1 *<1.53* <5.50 *<1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	<LLN to 4.0 *<LLN to 1.0*	3.6 to <4.0 *0.9 to <1.0*	3.2 to <3.6 *0.8 to <0.9*	<3.2 *<0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Creatine Kinase, High	3 to <6 x ULN	6 to <10 x ULN	10 to <20 x ULN	≥20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	>1.3 to 1.8 x ULN OR Increase of >0.3 mg/dL above baseline	>1.8 to <3.5 x ULN OR Increase of 1.5 to <2.0 x above baseline	≥3.5 x ULN OR Increase of ≥2.0 x above baseline
Creatinine Clearance[15] or eGFR, Low *Report only one*	NA	<90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to <30% decrease from baseline	<60 to 30ml/min or ml/min/1.73 m^2 OR ≥30 to <50% decrease from baseline	<30 ml/min or ml/min/1.73 m^2 OR ≥50% decrease from baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High*** ***Nonfasting, High***	110 to 125 *6.11 to <6.95* 116 to 160 *6.44 to <8.89*	>125 to 250 *6.95 to <13.89* >160 to 250 *8.89 to <13.89*	>250 to 500 *13.89 to <27.75* >250 to 500 *13.89 to <27.75*	>500 *≥27.75* >500 *≥27.75*
Glucose, Low (mg/dL; *mmol/L*) *≥1 month of age* *<1 month of age*	55 to 64 *3.05 to 3.55* 50 to 54 *2.78 to 3.00*	40 to <55 *2.22 to <3.05* 40 to < 50 *2.22 to <2.78*	30 to <40 *1.67 to <2.22* 30 to <40 *1.67 to <2.22*	<30 *<1.67* < 30 *<1.67*
Lactate, High	ULN to <2.0 x ULN without acidosis	≥2.0 x ULN without acidosis	Increased lactate with pH <7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
Lipase, High	1.1 to <1.5 x ULN	1.5 to <3.0 x ULN	3.0 to <5.0 x ULN	≥5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *≥18 years of age* *<18 years of age* ***LDL, Fasting, High*** *≥18 years of age* *>2 to <18 years of age* ***Triglycerides, Fasting, High***	 200 to <240 *5.18 to <6.19* 170 to <200 *4.40 to <5.15* 130 to <160 *3.37 to <4.12* 110 to <130 *2.85 to <3.34* 150 to 300 *1.71 to 3.42*	 240 to <300 *6.19 to <7.77* 200 to <300 *5.15 to <7.77* 160 to <190 *4.12 to <4.90* 130 to <190 *3.34 to <4.90* >300 to 500 *>3.42 to 5.7*	 ≥300 *≥7.77* ≥300 *≥7.77* ≥190 *≥4.90* ≥190 *≥4.90* >500 to <1,000 *>5.7 to 11.4*	 NA NA NA NA >1,000 *>11.4*
Magnesium[16], Low (mEq/L; *mmol/L*)	1.2 to <1.4 *0.60 to <0.70*	0.9 to <1.2 *0.45 to <0.60*	0.6 to <0.9 *0.30 to <0.45*	<0.6 *<0.30*
Phosphate, Low (mg/dL; *mmol/L*) *>14 years of age* *1 to 14 years of age* *<1 year of age*	2.0 to < LLN *0.81 to < LLN* 3.0 to <3.5 *0.97 to <1.13* 3.5 to <4.5 *1.13 to <1.45*	1.4 to < 2.0 *0.65 to < 0.81* 2.5 to <3.0 *0.81 to <0.97* 2.5 to <3.5 *0.81 to <1.13*	1.0 to <1.4 *0.32 to <0.65* 1.5 to <2.5 *0.48 to <0.81* 1.5 to <2.5 *0.48 to <0.81*	<1.0 *<0.32* <1.5 *<0.48* <1.5 *<0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to <6.0 *5.6 to <6.0*	6.0 to <6.5 *6.0 to <6.5*	6.5 to <7.0 *6.5 to <7.0*	≥7.0 *≥7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to <3.4 *3.0 to <3.4*	2.5 to <3.0 *2.5 to <3.0*	2.0 to <2.5 *2.0 to <2.5*	<2.0 *<2.0*

[15] Use the applicable formula (ie, Cockcroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).
[16] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Sodium, High (mEq/L; *mmol/L*)	146 to <150 *146 to <150*	150 to <154 *150 to <154*	154 to <160 *154 to <160*	≥160 *≥160*
Sodium, Low (mEq/L; *mmol/L*)	130 to <135 *130 to <135*	125 to <130 *125 to <135*	121 to <125 *121 to <125*	≤120 *≤120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to <10.0 *0.45 to <0.59*	10.0 to <12.0 *0.59 to <0.71*	12.0 to <15.0 *0.71 to <0.89*	≥15.0 *≥0.89*

HEMATOLOGY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *>5 years of age (not HIV infected)*	300 to <400 *300 to <400*	200 to <300 *200 to <300*	100 to <200 *100 to <200*	<100 *<100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *>5 years of age (not HIV infected)*	600 to <650 *0.600 x 10^9 to <0.650 x 10^9*	500 to <600 *0.500 x 10^9 to <0.600 x 10^9*	350 to <500 *0.350 x10^9 to <0.500 x 10^9*	<350 *<0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *>7 days of age* *2 to 7 days of age* *≤1 day of age*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9* 1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9* 4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9* 1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9* 3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9* 750 to 999 *0.750 x 10^9 to 0.999 x 10^9* 1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	<400 *<0.400 x 10^9* <750 *<0.750 x 10^9* <1,500 *<1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to <200 *1.00 to <2.00* OR 0.75 to <1.00 x LLN	75 to <100 *0.75 to <1.00* OR ≥0.50 to <0.75 x LLN	50 to <75 *0.50 to <0.75* OR 0.25 to <0.50 x LLN	<50 *<0.50* OR <0.25 x LLN OR Associated with gross bleeding
Hemoglobin[17], Low (g/dL; *mmol/L*)[18] *≥13 years of age (male only)* *≥13 years of age (female only)* *57 days of age to <13 years of age (male and female)* *36 to 56 days of age (male and female)* *22 to 35 days of age (male and female)* *8 to ≤21 days of age (male and female)* *≤7 days of age (male and female)*	10.0 to 10.9 *6.19 to 6.76* 9.5 to 10.4 *5.88 to 6.48* 9.5 to 10.4 *5.88 to 6.48* 8.5 to 9.6 *5.26 to 5.99* 9.5 to 11.0 *5.88 to 6.86* 11.0 to 13.0 *6.81 to 8.10* 13.0 to 14.0 *8.05 to 8.72*	9.0 to <10.0 *5.57 to <6.19* 8.5 to <9.5 *5.25 to <5.88* 8.5 to <9.5 *5.25 to <5.88* 7.0 to <8.5 *4.32 to <5.26* 8.0 to <9.5 *4.94 to <5.88* 9.0 to <11.0 *5.57 to <6.81* 10.0 to <13.0 *6.19 to <8.05*	7.0 to <9.0 *4.34 to <5.57* 6.5 to <8.5 *4.03 to <5.25* 6.5 to <8.5 *4.03 to <5.25* 6.0 to <7.0 *3.72 to <4.32* 6.7 to <8.0 *4.15 to <4.94* 8.0 to <9.0 *4.96 to <5.57* 9.0 to <10.0 *5.59 to <6.19*	<7.0 *<4.34* <6.5 *<4.03* <6.5 *<4.03* <6.0 *<3.72* <6.7 *<4.15* <8.0 *<4.96* <9.0 *<5.59*
INR, High (not on anticoagulation therapy)	1.1 to <1.5 x ULN	1.5 to <2.0 x ULN	2.0 to <3.0 x ULN	≥3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to <10.0%	10.0 to <15.0%	15.0 to <20.0%	≥20.0%

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
PTT, High (not on anticoagulation therapy)	1.1 to <1.66 x ULN	1.66 to <2.33 x ULN	2.33 to <3.00 x ULN	≥3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to <124,999 *100.000 x 10^9 to <124.999 x 10^9*	50,000 to <100,000 *50.000 x 10^9 to <100.000 x 10^9*	25,000 to <50,000 *25.000 x 10^9 to <50.000 x 10^9*	<25,000 *<25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to <1.25 x ULN	1.25 to <1.50 x ULN	1.50 to <3.00 x ULN	≥3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*) *>7 days of age* *≤7 days of age*	 2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9* 5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	 1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9* 4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	 1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9* 2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	 <1,000 *<1.000 x 10^9* <2,500 *<2.500 x 10^9*

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

APPENDIX A: TOTAL BILIRUBIN TABLE FOR TERM AND PRETERM NEONATES

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

[19] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.
[20] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.
[21] Definitions: Term is defined as ≥37 weeks gestational age; near-term, as ≥35 weeks gestational age; preterm, as <35 weeks gestational age; and neonate, as 0 to 28 days of age.
AV = atrioventricular; BPAP = bilevel positive airway pressure; CPAB = continuous positive airway pressure; INR = international standardized ratio; LLN = lower limit of normal; NA = not applicable; PT = prothrombin time; PTT = partial thromboplastin time; QTc = corrected QT; SGPT = serum glutamic pyruvic transaminase; WHO = World Health Organisation

Attachment 2: Cardiovascular Safety – Abnormalities

ECG

All important abnormalities from the ECG readings will be listed.

Abnormality Code	ECG parameter			
	HR	PR	QRS	$QT_{corrected}$
Abnormalities on actual values				
Abnormally low	≤ 45 bpm	NAP	≤ 50 ms	-
Abnormally high	≥ 120 bpm	≥ 210 ms	≥ 120 ms	-
[450 ms, 480 ms]	-	-	-	450 ms< QTc ≤ 480 ms
[480 ms, 500 ms]	-	-	-	480 ms< QTc ≤ 500 ms
More than 500 ms	-	-	-	QTc > 500 ms
Abnormalities on changes from baseline				
[30; 60] ms	-	-	-	[30; 60] ms
> 60 ms	-	-	-	> 60 ms

For absolute QTc parameters the categories are defined based on the ICH E14 Guidance [a]

Vital Signs[b]

The following abnormalities will be defined for vital signs:

Abnormality Code	Vital Signs parameter		
	Pulse	DBP	SBP
Abnormalities on actual values			
Abnormally low	≤ 45 bpm≤ 50 bpm	≤ 50 mmHg	≤ 90 mmHg
Grade 1 or mild	-	> 90 mmHg - < 100 mmHg	> 140 mmHg - < 160 mmHg
Grade 2 or moderate	-	≥ 100 mmHg - < 110 mmHg	≥ 160 mmHg - < 180 mmHg
Grade 3 or severe	-	≥ 110 mmHg	≥ 180 mmHg
Abnormally high	≥ 120 bpm	-	-

[a] The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/ICH/2/04, May 2005.
[b] The classification of AEs related to hypotension and hypertension will be done according to the DAIDS grading scale (see also Attachment 1).

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): _____

Institution: Janssen Pharmaceutical K.K.

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

SIGNATURES

Signed by	Date	Justification
Akihiro Koh	03Feb2017, 08:45:27 AM, UTC	Document Approval