Official Title: AN OPEN-LABEL, MULTICENTER, EXTENSION STUDY OF AG-348 IN ADULT SUBJECTS WITH PYRUVATE KINASE DEFICIENCY PREVIOUSLY ENROLLED IN AG-348 STUDIES

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STATISTICAL ANALYSIS PLAN

AN OPEN-LABEL, MULTICENTER, EXTENSION STUDY OF AG-348 IN ADULT SUBJECTS WITH PYRUVATE KINASE DEFICIENCY PREVIOUSLY ENROLLED IN AG-348 STUDIES

AG348-C-011

Version: 1.0

Date: 24-Sep-2020

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Twice daily
BMI	Body mass index
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DXA	Dual-energy x-ray absorptiometry
EAS	Efficacy Analysis Set
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End of study
EOT	End of treatment
EPO	Erythropoietin
FAS	Full Analysis Set
Hb	Hemoglobin
HLT	High Level Term
HRQOL	Health-related quality of life
IC	Informed consent
LDH	Lactate dehydrogenase
LFT	Liver function test
CCI	[redacted]
LLN	Lower limit of normal
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
CCI	[redacted]

Abbreviation	Definition
PD	Pharmacodynamic
PK	Pyruvate kinase
PKDD	Pyruvate kinase deficiency diary
PKDIA	Pyruvate kinase deficiency impact assessment
PKR	Pyruvate kinase isoform R
PRO	Patient Reported Outcome
PT	Preferred Term
QD	Once-daily
QOD	Every Other Day
QTc	Heart-rate corrected QT interval
QTcB	Heart rate-corrected QT interval using the Bazett's formula
QTcF	Heart rate-corrected QT interval using the Fridericia's formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
CCI	CCI
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

1. VERSION HISTORY

This statistical analysis plan (SAP) describes the analysis associated with protocol AG348-C-011, Version 2.0 (dated 03-Oct-2019).

Table 1: Summary of Major Changes in Statistical Analysis Plan Amendments

Version	Version Date	Summary of Changes
1.0	24-Sep-2020	Original version.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study AG348-C-011 except for pharmacokinetic and pharmacodynamic (PD) data which will be described in a separate SAP. This document may modify the plans outlined in the protocol.

Subjects may continue AG-348 treatment for up to a maximum of 192 weeks in this extension study (not including the time required for completion of the recommended dose taper) until they meet study withdrawal criteria, or the study is closed. This extension study will end when all subjects have discontinued or completed the study, are lost to follow-up, or the Study Sponsor terminates the study.

The final clinical study report (CSR) will include all data up to the End of Study (EOS) for all subjects.

Additional analyses of the data may be performed for publication or regulatory reporting purposes. In the following sections, references to “data cutoff date/EOS date” are meant to indicate that the data cutoff date will be used for analyses to be reported in a CSR or for other regulatory reporting purposes before the end of the study, and the EOS date will be used for analyses to be reported in the final CSR.

3. TRIAL OBJECTIVES AND ENDPOINTS

3.1. Objectives

3.1.1. Primary Objective

The primary objective of the study is to evaluate the long-term safety and tolerability of AG-348.

3.1.2. Secondary Objectives

Secondary objectives of the study are as follows:

- To evaluate the long-term efficacy of AG-348
- To evaluate the efficacy of AG-348 in increasing Hb concentrations in subjects who previously received placebo in Study AG348-C-006 (Cohort 1 only)

- To determine the effect of AG-348 on health-related quality of life (HRQoL) using patient reported outcomes (PROs)
- To evaluate the pharmacokinetics of AG-348 after oral administration (*Cohort 1 only*)
- To evaluate the relationship between AG-348 pharmacokinetics and safety parameters (*Cohort 1 only*)

CCI [redacted]

3.2. Endpoints

The baseline value is defined as the most recent measurement(s) before the first dose of AG-348, considering both the antecedent study and this extension study, unless otherwise specified in subsequent sections.

3.2.1. Primary Endpoint

The primary endpoint is to assess the long-term safety and tolerability of AG-348 by:

- Type, incidence, severity, and relationship to study drug of treatment-emergent adverse events (TEAEs); serious adverse events (SAEs); adverse events of special interest (AESIs); and TEAEs leading to dose reduction, treatment interruption, and treatment discontinuation
- Changes from baseline in clinical laboratory tests (ie, serum chemistry, liver function tests [LFTs], hematology, lipids, sex steroids, coagulation, urinalysis), physical examination (PE) findings, bone mineral density T- and Z-scores (total hip, femoral neck, and lumbar spine), vital signs, and 12-lead electrocardiogram (ECG) data

3.2.2. Secondary Endpoints

The secondary endpoints of the study are as follows:

- Cohort 1 only:
  - Proportion of subjects achieving a hemoglobin response, defined as a ≥1.5 g/dL (0.93 mmol/L) increase in Hb concentration from baseline that is sustained at 2 or more scheduled assessments at Weeks 16, 20, and 24
  - Average change from baseline in Hb concentration at Weeks 16, 20, and 24

  - Pharmacokinetic endpoints, including plasma concentrations over time and pharmacokinetic parameters of AG-348 (eg, AUC, C_{max}, others as applicable)
  - Exposure-response relationship between safety parameters and AG-348 concentration and relevant AG-348 pharmacokinetic parameters
- All cohorts:
  - Change from baseline in Hb concentration
  - Change from baseline in markers of hemolysis: bilirubin, lactate dehydrogenase (LDH), and haptoglobin levels
  - Change from baseline in markers of erythropoietic activity: reticulocyte percentages
  - Change from baseline in the number of transfusion events
  - Change from baseline in the number of red blood cell (RBC) units transfused
  - Change from baseline in HRQoL PRO scores: Pyruvate Kinase Deficiency Diary (PKDD) and Pyruvate Kinase Deficiency Impact Assessment (PKDIA)

CCI [redacted]

4. STUDY DESIGN

This is a multicenter, open-label, extension study to evaluate the long-term safety, tolerability, and efficacy of treatment with AG348 (hereinafter referred to as mitapivat) in subjects who were previously enrolled in Study AG348-C-006 or Study AG348-C-007.

Subjects will be assigned to 1 of the following 3 cohorts, depending on the antecedent study and the previous treatment received in the antecedent study:

- Cohort 1: Subjects who received placebo in Study AG348-C-006
- Cohort 2: Subjects who received mitapivat in Study AG348-C-006
- Cohort 3: Subjects who received mitapivat in Study AG348-C-007

To be eligible to receive mitapivat in AG348-C-011 subjects must have completed the antecedent AG-348 study.

For all cohorts, subjects may continue mitapivat treatment up to a maximum of 192 weeks (not including the time required for completion of the recommended dose taper) in this extension study.

Cohort 1:

The first visit of this extension study should coincide with the last visit of Study AG348-C-006. After completion of all scheduled assessments at the subject's last visit of Study AG348-C-006 and before the start of study drug in this extension study, the subject, Investigator, and site personnel will be unblinded to the Study AG348-C-006 treatment allocation of the subject, and the Investigator will determine whether the subject meets all eligibility criteria of this extension study. Following enrollment in this extension study, subjects in Cohort 1 will participate in a 12-week Dose Optimization Period followed by a 12-week Fixed Dose Period. The dose the subject is prescribed at the Week 12 Visit will be considered the subject's optimized dose and will be the dose the subject receives during the Fixed Dose Period (unless a dose modification is required for reasons related to safety). Following completion of the Fixed Dose Period, subjects will continue the mitapivat dose regimen they were receiving at the Week 24 Visit (unless a dose modification is required for reasons related to safety).

Cohort 2:

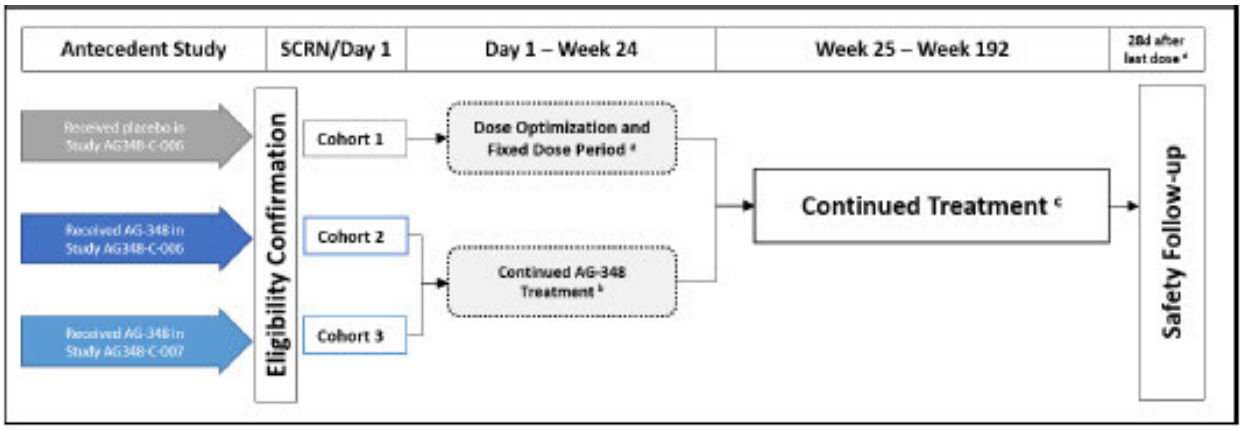
The first visit of this extension study should coincide with the last visit of Study AG348-C-006. After completion of all scheduled assessments at the subject's last visit of Study AG348-C-006 and before the start of study drug in this extension study, the subject, Investigator, and site personnel will be unblinded to the Study AG348-C-006 treatment allocation of the subject, and the Investigator will determine whether the subject meets all eligibility criteria of this extension study. Subjects will continue the mitapivat dose regimen they were receiving at the Week 24 Visit of Study AG348-C-006 (unless a dose modification is required for reasons related to safety).

Cohort 3:

The first visit of this extension study should coincide with the last visit of Study AG348-C-007. After completion of all scheduled assessments at the subject's last visit of Study AG348-C-007 and before the start of study drug in this extension study, the Investigator will determine whether the subject meets all eligibility criteria of this extension study. Subjects will continue the mitapivat dose regimen they were receiving at the Part 2 Week 24 Visit of Study AG348-C-007 (unless a dose modification is required for reasons related to safety).

An overview of the study design is provided in Figure 1.

Figure 1: Overview of Design for Study AG348-C-011



Abbreviations: d = day; SCRN = Screening.
[a] Eligible subjects in Cohort 1 will initiate treatment with AG-348 in this extension study. Therefore, these subjects will participate in a 12-week Dose Optimization Period followed by a 12-week Fixed Dose Period during the first 24 weeks of this extension study.
[b] Subjects who are in Cohort 2 or 3 will continue AG-348 treatment.
[c] Dosing between Week 24 and Week 25 is continuous.
[d] All subjects who permanently discontinue AG-348 at any time will attend a Safety Follow-up Visit 28 days (±4 days) after the last dose of AG-348 (including the time required to dose taper).

5. ANALYSIS DATA SETS

Only subjects who sign informed consent and are screened will be included in the analysis sets below.

- The Full Analysis Set (FAS) will include all subjects who receive at least 1 dose of study treatment.
- The Safety Analysis Set will include all subjects who receive at least 1 dose of study treatment. In this non-randomized study, the FAS and the safety analysis set are identical.
- The Efficacy Analysis Set (EAS) is a subset of the FAS and will include all subjects in Cohort 1 who receive the first dose of mitapivat more than 24 weeks (≥169 days) before the data cutoff date. This data set will only be used for reporting of efficacy data prior to EOS.

Table 2 summarizes the use of the analysis sets.

Table 2: Analysis Sets for Each Endpoint

Endpoints	Full Analysis Set (FAS)	Safety Analysis Set	Efficacy Analysis Set (EAS)
Demographic and other baseline characteristics	✓		✓
Disposition	✓		✓
Major protocol deviations	✓		
Exposure and concomitant therapies		✓	
Efficacy	✓		✓
Safety		✓	

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. Randomization, Blinding, Unblinding, and Crossover

This is a non-randomized, open-label study. Subjects will be assigned to 1 of the following 3 cohorts, depending on the antecedent study and the previous treatment received in the antecedent study:

- Cohort 1: Subjects who received placebo in Study AG348-C-006
- Cohort 2: Subjects who received mitapivat in Study AG348-C-006
- Cohort 3: Subjects who received mitapivat in Study AG348-C-007

For Cohorts 1 and 2, the first visit of this extension study should coincide with the last visit of Study AG348-C-006. After completion of all scheduled assessments at the subject's last visit of Study AG348-C-006 and before the start of study drug in this extension study, the subject, Investigator, and site personnel will be unblinded to the Study AG348-C-006 treatment allocation of the subject.

6.2. Sample Size Determination and Decision Rules

6.2.1. Sample Size Determination

Up to 116 subjects are potentially eligible to be enrolled into this extension study including 76 subjects from Study AG348-C-006 and 20 to 40 subjects from Study AG348-C-007.

The primary objective of the study is associated with safety. Table 3 provides the 95% exact confidence intervals (CIs) assuming different observed incidence of AEs.

Table 3: 95% Exact Confidence Intervals Assuming Different Observed Incidence Probability of Observing at Least 1 Specific AE Given Different Underlying AE Incidence Rates

Observed Incidence of Adverse Events, n (%) N=116	95% Exact CI
10 (8.6%)	(4.2, 15.3)
20 (17.2%)	(10.9, 25.4)
30 (25.9%)	(18.2, 34.8)
40 (34.5%)	(25.9, 43.9)

6.2.2. Decision Rules

There are no formal statistical decision rules in this study.

6.3. Definitions

6.3.1. Study Drug and Study Treatment

Both study drug and study treatment are defined as mitapivat.

6.3.2. Start and End Dates of Study Drug and Study Treatment

The **start of study treatment** is the earliest date/time of administration of a non-zero dose of the study treatment in this study.

The **end of study treatment** is the latest date of administration of a non-zero dose of the study treatment on or before the data cutoff date/EOS date.

6.3.3. Study Day

The study day for assessments or events occurring on or after the start of study treatment (eg, AE onset, laboratory assessment) will be calculated as:

Study day = Date of the assessment or event − start of study treatment + 1.

The study day for assessments or events occurring before the start of study treatment (eg, laboratory assessment during the Screening Period, medical history) will be negative and calculated as:

Study day = Date of the assessment or event − start of study treatment.

There is no study day 0. The study day will be displayed in data listings.

6.3.4. Baseline

Efficacy Evaluations

For efficacy CCI [redacted] laboratory parameters [Hb, hemolysis markers (indirect bilirubin, LDH, haptoglobin), reticulocyte percentage CCI [redacted] CCI [redacted]], baseline is defined as follows.

- For Cohort 1, the baseline value will be derived following the same rules as those outlined in Study AG348-C-006 but considering start of mitapivat in Study AG348-C-011 as the reference instead of the date of randomization in Study AG348-C-006. Namely,
  - The baseline is the average of all available measurements from the central laboratory within 45 (42+3) days before start of study treatment in AG348-C-011.
  - Assessments collected within 61 days after a transfusion will be excluded from the baseline derivations.
  - Baseline will be derived based on central laboratory data; if no central laboratory data are available before the start of study treatment, then local laboratory data will be used to derive the baseline.
- For Cohort 2, the baseline value from AG348-C-006 will be used.
- For Cohort 3, the baseline value from AG348-C-007 will be used.

For HRQOL assessments baseline is defined as follows.

- For Cohort 1, the baseline value will be derived following the same rules as those outlined in Study AG348-C-006 but considering start of mitapivat in Study AG348-C-011 as the reference instead of start of study treatment in Study AG348-C-006. Namely, for HRQOL assessments (except for PKDD), the last measurement before the start of study treatment in AG348-C-011 will be used as the baseline. For PKDD, baseline of weekly mean score is defined as the average of daily scores collected within 7 days before the start of study treatment in AG348-C-011
- For Cohort 2, the baseline value from AG348-C-006 will be used.
- For Cohort 3, the baseline value from AG348-C-007 will be used.

Safety Evaluations and Baseline Characteristics

For alanine aminotransferase (ALT) and aspartate aminotransferase (AST), baseline is defined as follows.

- For Cohort 1, the baseline value will be derived following the same rules as those outlined in Study AG348-C-006 but considering start of mitapivat in Study AG348-C-011 as the reference instead of start of study treatment in Study AG348-C-006. Namely,
  - The baseline is the average of all screening assessments collected within 45 (42+3) days before the start of study treatment in AG348-C-011.
  - Baseline will be derived based on central laboratory data; if no central laboratory data are available before the start of study treatment, then local laboratory data will be used to derive the baseline.
- For Cohort 2, the baseline value from AG348-C-006 will be used.
- For Cohort 3, the baseline value from AG348-C-007 will be used.

For other laboratory assessments:

- Prior to deriving the baseline,
  - If there are multiple records with the same assessment day and time from the same laboratory, the average value will be used
  - If there are multiple records with the same assessment day and time from different laboratories, the value from the central laboratory will be used
- The baseline will then be the last value on or before the start of study treatment (in AG348-C-011 for Cohort 1, in AG348-C-006 for Cohort 2, and in AG348-C-007 for Cohort 3).

Triplicate ECGs are collected in the study; the baseline for each ECG measurement is the average of the last predose replicate measurements on or before the start of study treatment (in AG348-C-011 for Cohort 1, in AG348-C-006 for Cohort 2, and in AG348-C-007 for Cohort 3). Unscheduled assessments will not be included in the calculation of the average. The average of the replicate measurements will be determined after the derivation of the individual parameter at each time point.

For all other parameters except age, the last assessment on or before the start of study treatment (in AG348-C-011 for Cohort 1, in AG348-C-006 for Cohort 2, and in AG348-C-007 for Cohort 3) will be used as the baseline. The baseline age will be calculated based on the data of informed consent (IC) in antecedent study (Section 6.4.2)

If, per protocol, an assessment (efficacy, safety, or baseline characteristics) is to be performed on study day 1, before the first dose of study treatment, and the assessment time, time of first dose of study treatment, or both, is missing (or not collected), it will be assumed that the assessment is performed before study treatment administration. Unscheduled assessments will be used in the determination of baseline; however, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

If no assessment meets the definition of baseline for an evaluation (efficacy, safety, or baseline characteristics),

- Cohort 1: the baseline value from AG348-C-006 will be used
- Cohorts 2 and 3: the baseline will be set to missing

6.3.5. On-Treatment Period and Optimized Dose

The **on-treatment period** starts on the date of start of study treatment in AG348-C-011 and ends 28 days after the end of study treatment. Within the on-treatment period the following dosing periods (Dose Optimization Period, Fixed Dose Period, Dose Taper Period) are defined:

- For Cohort 1, the dosing periods will be derived following the same rules as those outlined in Study AG348-C-006 but considering the date of start of mitapivat in Study AG348-C-011 as the reference instead of the date of start of study treatment in Study AG348-C-006. Namely,

- **Dose Optimization Period** starts on the date of start of study treatment in AG348-C-011 and ends on the date of the mitapivat dose administered at the Week 12 Visit or the earliest date of EOS, the end of the on-treatment period, and the first day of the dose taper prescription if a subject discontinued the study before reaching the Week 12 Visit.
- **Fixed Dose Period** starts 1 day after the end of the Dose Optimization Period and ends on the first day of the dose taper prescription if the subject enters the dose taper period or 4 days after the end of study treatment otherwise. Note that the Fixed Dose Period will not end at Week 24 in Study AG348-C-011 since subjects may continue to receive the optimized dose of mitapivat beyond Week 24.
- **Dose Taper Period** starts 1 day after the first day of the dose taper prescription and ends on the date of the earlier date of EOS and the end of on-treatment period. This period is only applicable to subjects who went through the dose taper.

- For Cohorts 2 and 3
  - **Dose Optimization Period**, based on the eligibility criteria, must be completed in the antecedent study.
  - **Fixed Dose Period**, based on the eligibility criteria, must be initiated in the antecedent study, continues in this study and ends on
    - the first day of the dose taper prescription if the subject enters the dose taper period, or
    - 4 days after the end of study treatment otherwise.
  - **Dose Taper Period**,
    - Starts 1 day after the first day of the dose taper prescription
    - Ends on the date of the earlier date of EOS and the end of on-treatment period

    This period is only applicable to subjects who went through the dose taper.

The **optimized dose** is defined as follows:

- For Cohort 1, the optimized dose will be derived following the same rules as those outlined in Study AG348-C-006 but considering the dose prescribed at the Week 12 visit in AG348-C-011 instead of the dose prescribed at the Week 12 visit in AG348-C-006.
- For Cohorts 2 and 3, since the eligibility criteria for AG348-C-011 requires that subjects must have completed the Dose Optimization Period in the antecedent study, the optimized dose is the dose prescribed at the start of AG348-C-011.

Data listings will include all assessments and events, with those that occur outside of the on-treatment period flagged.

6.4. General Methods

6.4.1. Data Handling After Cutoff Date

For analyses of the data prior to EOS, the data after the cutoff date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

6.4.2. Standard Derivations and Reporting Conventions

The following conversion factors will be used to convert days into weeks, months, or years: 1 week=7 days, 1 month=30.4375 days, and 1 year=365.25 days.

The following derivations will be implemented:

- Age (years)=(year of given informed consent in antecedent study − year of birth), since only year of birth is collected in the eCRF.

  The integer part of the calculated age will be used for reporting purposes.
- Body mass index (BMI; kg/m^2)=weight (kg)/height $(m)^2$
- Duration (in days) from a reference date (eg, start date of study treatment) =
  - date of event − reference date + 1, if the date of the event is on or after the reference date
  - date of event − reference date, if the date of the event is before the reference date

Reporting conventions will be as follows:

- Mean and median will be displayed to one more decimal place than the raw data.
- Standard deviation (SD) will be displayed to two more decimal places than the raw data.
- Percentages will be displayed to 1 decimal place (however, percentages corresponding to 0 counts will be reported as 0 rather than 0.0 and 100 percent will be reported as 100 rather than 100.0).
- Unless otherwise specified, rounding will be performed to the closest integer / first decimal using the common mid-point between the two consecutive values, eg, 5.11 to 5.14 will be rounded to 5.1, and 5.15 to 5.19 will be rounded to 5.2.
  - Non-zero percentages that are <0.1 before rounding will be displayed as "<0.1", eg, 0.09 will be reported as <0.1 rather than as 0.1.

6.4.3. Pooling of Data Across Sites

In order to provide overall estimates of treatment effects, data will be pooled across sites. The "site" factor will not be considered in statistical models or subgroup analyses given the high number of participating sites in contrast to the anticipated small number of subjects treated at each site.

6.4.4. Continuous and Categorical Variables

Continuous variables will be summarized using descriptive statistics, ie, number of non-missing values, mean, SD, median, quartiles, minimum, and maximum.

Categorical variables will be summarized by frequency distributions (number and percentage of subjects within a given category in the analysis data set). Unless otherwise specified, the calculation of percentages will include the "missing" category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category. For summaries by visit, percentages will be based on the number of subjects with data available for that visit, unless otherwise specified.

6.4.5. Unscheduled Visits

Generally, data collected at unscheduled visits will be included and summarized for both safety and efficacy analyses in the same manner as the data collected at scheduled visits. Data collected at unscheduled visits will be included in by-subject listings together with the data collected at scheduled visits.

Summaries of outliers (eg, worst value, worst change from baseline, worst Common Terminology Criteria for Adverse Events [CTCAE] grade) during the on-treatment period for safety endpoints such as laboratory measurements and ECG parameters will include data from both scheduled and unscheduled visits.

Individual longitudinal plots for laboratory measurements during the on-treatment period will include data from both scheduled and unscheduled visits.

Descriptive statistics (mean, SD, median, quartiles, minimum, maximum) by nominal visit will consider data of both scheduled and unscheduled visits. For efficacy and safety parameters [Hb, hemolysis markers (indirect bilirubin, LDH, haptoglobin), reticulocyte percentage, CCI DXA scans results, CCI CCI HRQOL endpoints], data collected at unscheduled and scheduled postbaseline visits will be mapped to scheduled visits using analysis visit windows, and then values at scheduled postbaseline visits will be derived based on the rules described below. Descriptive statistics by nominal visit and longitudinal plots during the on-treatment period for efficacy endpoints such as Hb concentration will be provided using the derived values at scheduled visits.

Analysis Visit Windows

For the evaluation of Hb, hemolysis markers (indirect bilirubin, LDH, and haptoglobin), reticulocyte percentage, CCI DXA scans results, CCI CCI and HRQOL endpoints, the analysis visit windows will be derived based on the target study day for the scheduled visits as follows. Note that based on the scheduled of assessments, a Week n Visit, will have a target study day of 1+(n×7). For example, the Week 4 visit will have a target study day of 1+(4×7)=29.

- Visit windows will be implemented for scheduled visits after Day 1.
- For analysis visit(n):

  - Start day of visit window =1+end day of window for visit(n−1). If n=1, start day of the visit window is study day 2
  - End day of visit window = [(target day for analysis visit(n) + target day for analysis visit(n+1))/2]–1 except for the last scheduled visit. The end day of the last scheduled visit is the end of Fixed Dose Period for Hb, hemolysis markers (indirect bilirubin, LDH, and haptoglobin), reticulocyte percentage, CCI and HRQOL endpoints

- For DXA scan results CCI the analysis visit window for the Week 24 Visit will start on study day 86. The derivation for the end day of Week 24 Visit and the remaining visit windows will follow the same rule of deriving "analysis visit(n)" specified above, except that the end day of the last visit window on or before the data cutoff date is the cutoff date/EOS date.

Derivation of Values at Scheduled Postbaseline Visits Based on Analysis Visit Windows

Cohorts 1 and 2:

- For laboratory parameters including Hb, hemolysis markers, reticulocyte percentage, CCI analysis visit window and derived value at scheduled visit will be derived. Any assessments obtained within 61 days after a transfusion will be excluded derivation. In addition:
  - Central laboratory assessment(s) (scheduled or unscheduled) within the visit windows will be used
  - If no central laboratory value is within the visit window, local laboratory assessment(s) within the visit window will be used

All cohorts

- For HRQOL data, assessments (scheduled or unscheduled) within the visit windows and on or before the end of the Fixed Dose Period will be used.
- If multiple assessments are identified within a visit window for a parameter, the following rules will be applied:
  - The assessment measured closest to the target study day of the scheduled visit will be used
  - If there are multiple assessments equidistant to the target study day
    - the average value will be used for efficacy laboratory parameters
    - the later assessment will be used for HRQOL endpoints

6.5. Methods for Handling Missing Data

6.5.1. Adverse Event and Concomitant Medication Start Dates

If the end date is non-missing and the imputed start date is after the end date, the end date will be used as the start date.

(1) Missing day only

- If the month and year are the same as the month and year of the date of the start of study treatment, the date of the start of study treatment will be used.
- If the month and year are before the month and year of the date of the start of study treatment, the last day of the month will be used.
- If the month and year are after the month and year of the date of the start of study treatment, the first day of the month will be used.

(2) Missing day and month

- If the year is the same as the year of the date of the start of study treatment, the date of the start of study treatment will be used.
- If the year is before the year of the date of the start of study treatment, 31 December will be used.
- If the year is after the year of the date of the start of study treatment, 01 January will be used.

(3) Missing day, month, and year

- The date of the start of study treatment will be used.

6.5.2. Adverse Event and Concomitant Medication End Dates

If the start date is non-missing and the imputed end date is before the start date, the start date will be used as the end date. If an imputation for an AE end date results in an AE end date that is after the data cutoff date/EOS date, the AE will be considered as ongoing at the data cutoff date/EOS date.

(1) Missing day only

- The last day of the month will be used.

(2) Missing day and month

- 31 December will be used.

(3) Missing day, month, and year

- The event will be regarded as ongoing.

6.5.3. Exposure

No imputation will be done for the date of the first dose of study drug.

If the date of the last dose of study drug is missing or partially missing, it will be imputed as follows (separately for each study drug):

- If the last date of study drug is completely missing and there is no End of Treatment Disposition eCRF page for the study drug AND there is no death date, the subject should be considered to be ongoing and the data cutoff date/EOS date for the analysis will be used as the last dosing date.

- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment Disposition eCRF page for the study drug OR a death date (on or before the data cutoff date/EOS date), then the imputed last dose date is:

  =Last day of the year, if only the year is available and Year <Year of min(EOT date, death date)

  =Last day of the month, if both the year and month are available and Year=Year of min(EOT date, death date) and Month <Month of min(EOT date, death date)

  =min(EOT date, death date), for all other cases

7. STATISTICAL ANALYSES

All summaries will be tabulated by cohort and overall, unless otherwise specified. Summaries of efficacy [redacted] endpoints will be tabulated only by cohort.

7.1. Subject Disposition

The frequency of subjects in each of the analysis sets described in Section 5 will be summarized.

The following summaries will be presented based on the FAS (or based on the EAS for analysis of the data prior to EOS):

- Frequency of subjects treated in each geographic region, country, and site
- Frequency of subjects with study drug ongoing
- Frequency of subjects who discontinued study drug, overall and by the reason for discontinuation of study drug
- Frequency of subjects who completed the study
- Frequency of subjects ongoing in the study
- Frequency of subjects who discontinued the study, overall and by the reason for study discontinuation

The frequency of subjects with disposition reason, in each epoch, due to reasons associated with COVID-19 will further be summarized under the main reason for discontinuation.

Disposition for all treated subjects will be provided in by-subject listings.

7.2. Protocol Deviations

All major protocol deviations that impact the safety of the subjects, the conduct of the study or the evaluation of the study results will be reported based on the FAS. These will include:

- Subjects treated despite not satisfying the eligibility criteria
- Subjects who develop withdrawal criteria while on the study but are not withdrawn

- Subjects who receive an excluded concomitant medication

In addition, for each category of major protocol deviations, those related to COVID-19 will be summarized.

Major protocol deviations will be provided in a by-subject listing.

7.3. Demographic and Other Baseline Characteristics

The following summaries will be presented by cohort and overall based on the FAS (or based on the EAS for analyses of the data prior to EOS).

7.3.1. Demographics and Physical Measurements

Demographic characteristics and physical measurements at baseline will be summarized as follows:

- Demographic characteristics
  - Sex: male, female (child-bearing potential status will be summarized for female subjects)
  - Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, other, unknown
  - Ethnic origin: Hispanic or Latino, not Hispanic or Latino, not reported
  - Age (years): summary statistics
- Age categories:
  - <65, ≥65 years
  - <35, ≥35 years
- Physical measurements
  - Height (cm)
  - Weight (kg)
  - BMI (kg/m^2)

Demographic data for all screened subjects will be provided in a by-subject listing.

7.3.2. Disease Characteristics

The following baseline characteristics of the underlying disease will be summarized:

- Baseline Hb concentration [both continuously and by categories (<8.5 g/dL, ≥8.5 g/dL)]
- Prior splenectomy status (Yes, No; if Yes, age of splenectomy)
- Prior chelation status (Yes, No); the status is "Yes" if a subject has received chelation therapy within 52 weeks (364 days) prior to the first dose of study treatment.

- Prior cholecystectomy status (Yes, No; if Yes, age of cholecystectomy)
- PKLR gene mutation status (missense/missense, missense/non-missense)
- DXA scan results by location (femoral total and adjusted spine): Bone mineral density (BMD) and corresponding T-scores and Z-scores. Frequency of subjects with T-scores in 3 categories (≤−2.5, >−2.5-<−1.0, ≥−1.0)

Data on disease characteristics will be provided in by-subject listings.

7.4. Exposure to Study Drug and Compliance

The following summaries will be presented based on the safety analysis set.

7.4.1. Treatment Duration and Exposure

The frequency of subjects with an optimized dose of 5 mg BID, 20 mg BID or 50 mg BID will be summarized.

Duration of exposure will be summarized as a continuous variable as well as in categories (>0-4, >4-8, >8-12, >12-16, >16-20, >20-24, and in 12-week intervals beyond 24 weeks).

Study drug compliance will be summarized based on percentage of tablets taken, where

- Percentage of tablets taken = 100×(total number of tablets administered)/(total number of tablets intended)
- Total number of tablets administered = total number of tablets dispensed − tablets returned
- Duration of prescription = end date of prescription – start date of prescription +1
- Number of tablets intended during each prescription: for each new prescription, prescribed dosing frequency × duration of the prescription. Prescribed dosing frequency takes value of 0.5, 1, and 2 for every other day (QOD), once daily (QD) and twice daily (BID), respectively.
- Total number of tablets intended = sum of number of tablets intended over all prescriptions.

Percentage of tablets taken will be summarized. The frequency of subjects whose compliance is <80%, 80-100%, >100-120%, and >120% will be summarized.

7.4.2. Dose Modifications

The summary of dose modifications will include:

- The frequency of subjects with at least 1 dose reduction
- Summary of reasons for dose reduction

Dose reduction is defined as the prescribed dose being decreased from the previous dose collected in the Prescribed Dose eCRF. Dose prescriptions and modifications will be provided in a by-subject listing.

7.5. Concomitant Therapies

The following summaries will be presented based on the safety analysis set.

Concomitant medications are defined as non-study medications (from the Concomitant Medications eCRF) that are started during the on-treatment period or are started before the start of the study treatment and end or remain ongoing during the on-treatment period.

All non-study medications will be coded according to ATC code and PT using the latest version of the WHO Drug Dictionary. All concomitant medications will be summarized in frequency tabulations according to WHO ATC third level and PT.

Concomitant procedures are defined as procedures (from the Concomitant Procedures eCRF) that are started during the on-treatment period or are started before the start of the study treatment and end or remain ongoing during the on-treatment period.

The concomitant procedures will be coded by the latest version of MedDRA by SOC and PT and will be summarized in frequency tabulations by SOC and PT.

Concomitant transfusions are collected in the "On Study Transfusions" eCRF page.

Concomitant transfusions will be provided in a by-subject listing.

7.6. Efficacy Analyses

All efficacy analyses will be performed separately for each cohort based on the FAS, unless otherwise specified.

7.6.1. Hemoglobin Response in Cohort 1

Hb Response is defined as a ≥1.5 g/dL increase in Hb concentration from baseline that is sustained at 2 or more scheduled assessments at Weeks 16, 20, and 24 during the Fixed Dose Period. Subjects with missing Hb assessment(s) over Weeks 16, 20, and 24 and who did not obtain 2 assessments with ≥1.5 g/dL increase from baseline will be considered as non-responders. The details for derivation of Hb at baseline and postbaseline visits are provided in Sections 6.3.4 and 6.4.5.

For analysis of the data prior to EOS, the frequency of Hb responders will be summarized based on the EAS instead of the FAS.

7.6.2. Average Change from Baseline in Hb Concentration at Weeks 16, 20, and 24 in Cohort 1

The average change from baseline at Weeks 16, 20, and 24 will be summarized for Cohort 1. For analysis of the data prior to EOS, the summaries will be based on the EAS instead of the FAS.

7.6.3. Hemoglobin Concentrations and Other Clinical Activity Indicators

For Hb concentrations, hemolysis markers (indirect bilirubin, LDH, and haptoglobin), and reticulocyte percentage, the following summaries and figures will be provided for Cohorts 1 and 2 based on the FAS. For analysis of the data prior to EOS, the summaries for Cohort 1 will also be tabulated based on the EAS.

- Summary of data by visit
- A longitudinal plot of mean value (+/-SD) at each visit for Hb and hemolysis markers.

For all cohorts, by-subject longitudinal plots will be presented with markers of hemolysis at baseline and scheduled visits, transfusion and prescribed dose over time; the plots will further include optimized dose, age, sex, race, PKLR gene mutation category, baseline Hb concentration, prior splenectomy status, baseline chelation status, and postbaseline chelation status.

7.6.4. Change from Baseline in the Number of Transfusion Events

Number of transfusions at baseline will be determined based on the transfusion data during the 52 weeks before IC of this study for Cohort 1 and 52 weeks before IC of the antecedent study for Cohort 2 and Cohort 3. Number of on-study transfusions will be based on transfusions collected up to the end of Fixed Dose Period and standardized to 52 weeks. The change from baseline in number of transfusions will be summarized.

7.6.5. Change from Baseline in the Number of RBC Units Transferred

Number of RBC units at baseline are only collected for Cohort 3 and will be determined based on the transfusion data during the 52 weeks before IC of the antecedent study for Cohort 3. Number of on-study RBC units will be based on transfusion data collected up to the end of Fixed Dose Period and standardized to 52 weeks. The change from baseline in number of transfusions will be summarized.

7.6.6. HRQOL Measurements

7.6.6.1. Pyruvate Kinase Deficiency Diary (PKDD)

PKDD is a self-administered, daily, 7-item PRO measure of the core signs and symptoms of PKD in adults. The PKDD daily scores will be calculated based on the subject's response to the PKDD questionnaire.

The daily PKDD scores summarized into weekly mean scores will be calculated and change from baseline in weekly mean scores will be summarized descriptively by week for the first 24 weeks for subjects in Cohort 1.

Data collected for subjects in Cohort 2 and 3, and data collected after week 24 visit for subjects in Cohort 1 will be summarized descriptively by visit.

7.6.6.2. Pyruvate Kinase Deficiency Impact Assessment (PKDIA)

The PKDIA is a 12-item PRO measure of the common impacts of PK deficiency on activities of daily living. Subjects rate how PK deficiency has impacted aspects of daily living in the past 7 days, including impacts on relationships; perceived appearance; work performance; and leisure, social, mental, and physical activities.

The PKDIA score at each visit will be calculated based on the subject's response to the PKDIA questionnaire.

The following summaries will be provided for PKDIA scores up to the end of the Fixed Dose Period at each visit:

- Summaries of scores for each item. For questions 9a, 11a and 12, the frequency of subjects with answers in each category will be summarized. For questions 9b and 11b, scores from patients who answered "Yes" will be summarized. For all the other questions, response will be treated as continuous variables and summarized
- PKDIA score and change from baseline

7.7. Safety Analyses

Summaries of safety data will be presented by cohort and overall based on the safety analysis set.

7.7.1. Adverse Events

Treatment-emergent adverse events (TEAEs) are AEs with a first onset date during the on-treatment period or worsening from baseline. All summaries described below will be based on TEAEs, if not otherwise specified.

All AEs will be listed by subject and AEs with onset outside of the on-treatment period will be flagged in the listings. Unless otherwise specified, TEAEs will be summarized according to the latest version of MedDRA by SOC and/or PT, severity (based on CTCAE v4.03 grading), seriousness, and relation to study treatment in decreasing frequency based on the frequencies observed overall.

Each subject will be counted only once within each SOC or PT. If a subject experiences multiple TEAEs under the same PT within a SOC for the same summary period, only the TEAE assessed as related or with the worst severity, as applicable, will be included in the summaries of relationship and severity. If a subject has TEAEs with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following will be summarized:

- TEAEs by SOC and PT
- TEAEs by SOC, PT, and worst grade
- Most common TEAEs and Grade ≥3 TEAEs by PT; these will include TEAEs (any grade) reported in ≥10% of subjects in any cohort or Grade ≥3 TEAEs reported in ≥5% of subjects in any cohort. These thresholds may be changed based on the observed data without an amendment to this SAP.
- Treatment-related TEAEs by SOC and PT
- Treatment-related TEAEs by SOC, PT, and worst grade
- Grade ≥3 TEAEs, by SOC and PT
- Treatment-related Grade ≥3 TEAEs, by SOC and PT

- Serious TEAEs by SOC and PT
- Treatment-related Serious TEAEs, by SOC and PT
- TEAEs leading to discontinuation of study drug, by SOC and PT
- TEAEs leading to interruption of study drug, by SOC and PT
- TEAEs leading to dose reduction, by SOC and PT
- TEAEs leading to death, by SOC and PT
- Treatment-related TEAEs leading to death, by SOC and PT

In addition, the following will be summarized by prescribed dose at TEAE onset.

- First occurrence of TEAEs by PT (Cohort 1 only)
- First occurrence of serious TEAEs by PT (Cohort 1 only)
- TEAEs by PT
- Serious TEAEs by PT

7.7.1.1. Adverse Events of Special Interest

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Additional TEAEs of interest for mitapivat are as follows:

- AEs of endocrinological interest (identified based on the criteria outlined in the mitapivat program specified Safety Search Criteria)
- Insomnia (PTs under HLT of "Disturbances in Initiating and Maintaining Sleep" or identified based on the criteria outlined in the mitapivat program specified Safety Search Criteria)

The following will be summarized for AESIs and the additional TEAEs of interest:

- AESIs/TEAEs of interest by PT
- AESIs/TEAEs of interest by PT and worst grade
- Grade ≥3 AESIs/TEAEs of interest by PT
- AESIs/TEAEs of interest leading to discontinuation of study drug by PT
- Serious AESIs/TEAEs of interest by PT
- AESIs/TEAEs of interest leading to death by PT

In addition, the following will be summarized by prescribed dose at TEAE onset for the additional AE of interest "Insomnia":

- First occurrence of TEAEs by PT
- First occurrence of serious TEAEs by PT

- TEAEs by PT
- Serious TEAEs by PT

7.7.1.2. Adverse Events Associated with COVID-19

The selection of AEs associated with COVID-19 will be based on the MedDRA MSSO list of PTs. The following will be summarized:

- TEAEs associated with COVID-19, by SOC and PT
- Grade ≥3 TEAEs associated with COVID-19, by SOC and PT
- Serious TEAEs associated with COVID-19, by SOC and PT
- TEAEs associated with COVID-19 leading to discontinuation of study drug, by SOC and PT
- TEAEs associated with COVID-19 leading to interruption of study drug, by SOC and PT
- TEAEs associated with COVID-19 leading to dose reduction, by SOC and PT
- TEAEs associated with COVID-19 leading to death, by SOC and PT

7.7.2. Death

The frequency of subjects in the safety analysis set who died will be tabulated based on information from the EOS eCRF. Deaths will be summarized for the following categories:

- On-treatment death: Deaths within 28 days after the last dose of study treatment (ie, deaths during the on-treatment period)
- Post-treatment death: Deaths more than 28 days after the last dose of study treatment (ie, deaths after the end of the on-treatment period)
- Overall: All deaths

In addition, deaths related to COVID-19 will be summarized.

Deaths for all screened subjects will be provided in a by-subject listing.

7.7.3. Clinical Laboratory Data

Clinical laboratory test results will be expressed in SI units. Preferred unit (g/dL) will also be used for Hb in efficacy analysis.

For each laboratory test (chemistry, hematology, coagulation) performed in the study, a by-subject listing of laboratory test results will be presented with the corresponding CTCAE grades (if applicable), laboratory normal ranges, and flags for values below lower limit of normal (LLN) or above upper limit of normal (ULN).

Parameters with CTCAE grades available:

Clinical laboratory test results will be graded according to CTCAE v4.03 as applicable. Grading will be derived based on the numerical thresholds defined by the CTCAE criteria.

Non-numerical qualifiers will not be taken into consideration in the derivation of CTCAE grading.

Laboratory test results classified according to CTCAE will be described using the worst grade. For parameters graded with 2 separate toxicity criteria, such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (eg, hypokalemia) grades at baseline and postbaseline will be set to 0 when the variables are derived for summarizing high direction toxicity (eg, hyperkalemia), and vice versa.

The frequency of subjects with laboratory toxicities during the on-treatment period will be tabulated as follows. The denominator used to calculate percentages for each laboratory test is the number of subjects evaluable for CTCAE grading for that parameter (ie, those subjects for whom a Grade of 0, 1, 2, 3 or 4 can be derived).

- The summary of laboratory parameters by CTCAE grade will include the number and percentage of subjects with Grade 1, 2, 3, 4; Grade 3-4; and Any Grade (Grades 1-4) during the on-treatment period. The highest CTCAE grade during the on-treatment period is considered the worst grade
- The shift table will summarize baseline CTCAE grade versus worst CTCAE grade during the on-treatment period. The highest CTCAE grade during the on-treatment period is considered the worst grade
- Newly occurring or worsening laboratory abnormalities (Any Grade, Grade 3-4) during the on-treatment period will also be summarized

Parameters with CTCAE grades not available:

Results of laboratory tests that are not part of CTCAE will be presented according to the following categories: below the LLN, within normal limits, and above the ULN according to the laboratory normal ranges.

Shift tables will display the frequency of subjects with shifts from baseline missing, <LLN, normal, or >ULN to each of <LLN, normal or >ULN during the on-treatment period.

7.7.3.1. Hematology

For **WBC differential counts** [total neutrophil, lymphocyte, monocyte, eosinophil, and basophil counts], the absolute value will be used when reported. When only percentages are available (relevant primarily for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

Derived differential absolute count=(WBC count)×(Differential % value/100)

If the range for the differential absolute count is not available (ie, the range is only available for the percentage) then Grade 1 will be attributed as follows:

- Lymphocyte count decreased:
  - Derived absolute count does not meet Grade 2-4 criteria, and
  - % value <% LLN value, and

- Derived absolute count ≥800/mm^3

- Neutrophil count decreased:
  - Derived absolute count does not meet Grade 2-4 criteria, and
  - % value<% LLN value, and
  - Derived absolute count ≥1,500/mm^3

7.7.3.2. Chemistry

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin are used to assess possible drug-induced liver toxicity. The ratios of test result to ULN will be calculated and categorized for these parameters during the on-treatment period.

The summary of liver function tests will include the following categories. The frequency of subjects with each of the following during the on-treatment period will be summarized:

- ALT >3×ULN, ALT >5×ULN, ALT >10×ULN, ALT >20×ULN
- AST >3×ULN, AST >5×ULN, AST >10×ULN, AST >20×ULN
- (ALT or AST) >3×ULN, (ALT or AST) >5×ULN, (ALT or AST) >10×ULN, (ALT or AST) >20×ULN
- total bilirubin >2×ULN
- Concurrent ALT >3×ULN and total bilirubin >2×ULN
- Concurrent AST >3×ULN and total bilirubin >2×ULN
- Concurrent (ALT or AST) >3×ULN and total bilirubin >2×ULN
- Concurrent (ALT or AST) >3×ULN and total bilirubin >2×ULN and ALP ≥2×ULN
- Concurrent (ALT or AST) >3×ULN and total bilirubin >2×ULN and (ALP <2×ULN or missing)

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a subject with an AST >10×ULN will also appear in the categories >5×ULN and >3×ULN. Liver function test elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will be created, with different symbols for different cohorts, by graphically displaying:

- Peak serum ALT (/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin=2×ULN
- Peak serum AST (/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin=2×ULN

In addition, the following individual longitudinal plots and by-subject listings will be provided:

- Individual longitudinal plot of ALT including subjects with at least one ALT during the on-treatment period >2.5×baseline or worsening to CTCAE Grade ≥2 during the on-treatment period
- Individual longitudinal plot of AST including subjects with at least one AST during the on-treatment period >2.5×baseline or worsening to CTCAE Grade ≥2 during the on-treatment period
- Listing of all total bilirubin, ALT, AST, and ALP values for subjects with a postbaseline total bilirubin >2×ULN, ALT >3×ULN, or AST >3×ULN
- Listing of all total bilirubin, indirect bilirubin, ALT, AST and ALP values for subjects with a postbaseline ALT >ULN or AST >ULN

In addition, a shift table from baseline to the worst CTCAE grade of ALT and AST during the on-treatment period will be provided. For each subject:

- If the worst CTCAE grade of ALT is worse than that of AST during the on-treatment period, the baseline CTCAE grade of ALT will be used
- If the worst CTCAE grade of AST is worse than that of ALT during the on-treatment period, the baseline CTCAE grade of AST will be used
- If AST and ALT have the same worst CTCAE grade during the on-treatment period, the lower baseline CTCAE grade of ALT and AST will be used

For **calcium**, CTCAE grading is based on corrected calcium and ionized calcium. Corrected Calcium is calculated from albumin and calcium as follows:

> Corrected calcium (mmol/L)=measured total calcium (mmol/L)+0.02×[40−serum albumin (g/L)]

7.7.3.3. Sex Steroid Tests

For sex steroid test results, shift tables will display the frequency of subjects with shifts from baseline missing, < LLN, normal, > ULN to each of < LLN, normal or > ULN during the on-treatment period.

In addition, individual longitudinal plots will be provided for each sex hormone by sex.

7.7.3.4. Pregnancy Test

Pregnancy test results will be presented in a by-subject listing.

7.7.4. Vital Signs and Physical Measurements

All physical measurements and vital sign assessments (height, weight, BMI, systolic blood pressure, diastolic blood pressure, pulse rate, temperature) will be presented in a by-subject listing.

7.7.5. Electrocardiograms

All ECG summaries and listings will be based on the central reading results.

ECG summaries will include all ECG assessments from the on-treatment period.

Selecting Primary QT Interval Correction for Heart Rate

The analysis of QT interval data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected QT interval, denoted QTc, which is independent of heart rate. This QTc is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis several of those methods of correction will be used, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

and the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds.

Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions.

ECG Summaries

The following analyses will be performed for each applicable ECG parameter (RR, PR, QRS, QT, and QTc) during the on-treatment period. The denominator used to calculate percentages for each category is the number of subjects evaluable for the category.

- Pearson correlation between QT and RR interval, QTc (QTcF, QTcB) and RR interval using individual (non-averaged) baseline assessments
- Frequency of subjects with notable ECG values, defined as those in the following categories:
  - QT/QTc interval increase from baseline >30 ms, >60 ms
  - QT/QTc interval > 450 ms, > 480 ms, > 500 ms
  - PR interval >200 ms
  - QRS duration >120 ms

All ECG assessments and qualitative ECG abnormalities will be presented in by-subject listings.

7.7.6. DXA Scans

DXA scan results including bone mineral density (BMD), T-scores, Z-scores during the on-treatment period will be summarized by location (total femur and adjusted spine), and visit. For T-scores, shift from baseline to the worst postbaseline results during the on-treatment period by category (≤-2.5, >-2.5 to <-1.0, ≥-1.0) will be provided.

All DXA scan results will be presented in a by-subject listing.

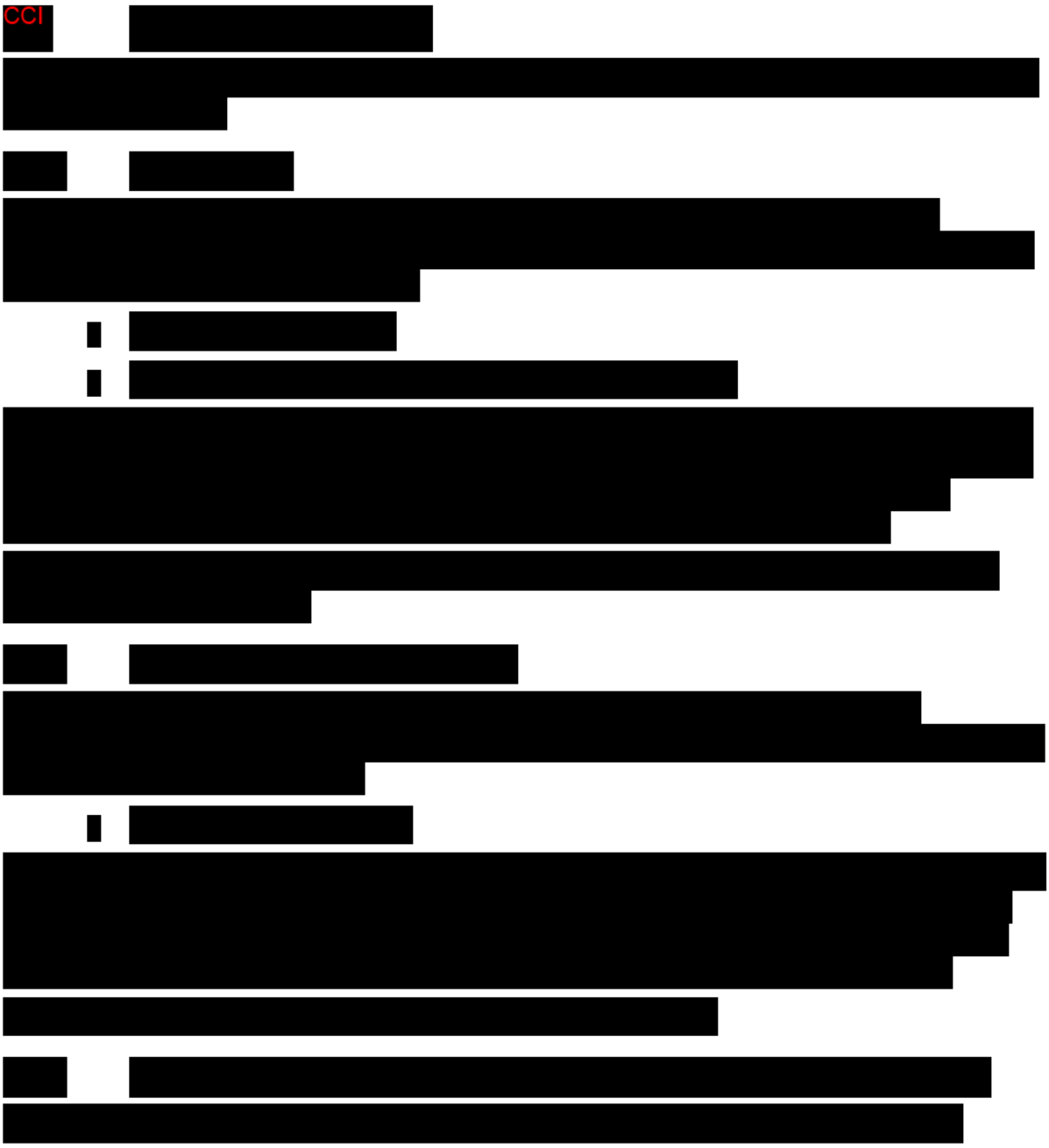
7.7.7. Menstrual Cycle Diary

Menstrual cycle diary data collected from women of childbearing potential during the on-treatment period will be summarized by regular contraceptive status (oral contraceptives or depot injection). The following summaries will be included:

- Total number of menstrual cycles reported
- Total number of abnormal menstrual cycles in the following categories: heavier, lighter, longer, shorter, sooner and later than usual.

Menstrual cycle diary data will be presented in a by-subject listing with regular contraceptive status flagged.

CCI [redacted]



CCI [redacted]

7.9. Interim Analyses

There is no interim analysis planned for this study.