27Oct2020

Re: Cover Letter for ClinicalTrials.gov NCT03036813 (Global Blood Therapeutics)

This Cover Letter accompanies Statistical Analysis Plan for this trial NCT03036813 which completed.

Sincerely,

DocuSigned by Margaret Tonda

Margaret Tonda | I approve this document 27-Oct-2020 | 15:02 PDT

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STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 3, Double-blinded, Randomized, Placebo-controlled, Multicenter Study of GBT440 (Voxelotor) Administered Orally to Patients With Sickle Cell Disease
Phase:	3
Protocol No.:	GBT440-031
Protocol Date	3 January 2019 **Amendment 4**
Analysis Plan Version and Date	Version 5.0, 3 January 2019

[redacted]

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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

[redacted]

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1. GLOSSARY OF ABBREVIATIONS

ACS	acute chest syndrome
AE	adverse event
BP	blood pressure
CGI	Clinical Global Impression
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOS	end of study
EOT	end of treatment
ePRO	electronic patient reported outcomes
EQ-5D-5L™	EuroQol EQ-5D-5L™ health questionnaire
GBT	Global Blood Therapeutics
Hb	hemoglobin
HbF	hemoglobin fetal
HbS	sickle hemoglobin
HbS $ß^0$ thal	sickle hemoglobin (S) and one beta thalassemia gene ($ß^0$ thal)
HbSC	heterozygous for hemoglobin S and hemoglobin C
HbSS	sickle hemoglobin with two sickle hemoglobin genes (SS)
Hct	hematocrit

HR	heart rate
HU	hydroxyurea
IA	Interim Analysis
ICF	informed consent form
ITT	intent to treat
IXRS	interactive response system
LDH	lactate dehydrogrenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MMRM	mixed effect model for repeated measures
NHLBI	National Heart, Lung, and Blood Institute
PASS	Power Analysis and Sample Size Software
PD	pharmacodynamics(s)
PK	pharmacokinetic(s)
PRO	patient reported outcome(s)
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SCDS	sickle cell disease severity
SCDSM	sickle cell disease severity measure
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TSS	Total Symptom Score
ULN	upper limit of normal
VOC	vaso-occlusive crisis
WHO	World Health Organization

2. INTRODUCTION

Global Blood Therapeutics (GBT) is conducting a Phase 3 study (Study GBT440-031) evaluating voxelotor for the treatment of sickle cell disease (SCD) in adult and adolescent patients with SCD. The study is being conducted in 3 groups (Group 1, Group 2 and Group 3) as described in the protocol. Group 1 and Group 2 have enrolled a total of 274 subjects including 46 adolescents. No subject has been enrolled in Group 3.

Description of Groups and analysis:

- Group 1 includes 62 subjects randomized 1:1:1 to voxelotor 900 mg or 1500 mg or to placebo. When the 62nd subject reached 12 weeks of treatment, data from the first 62 subjects were unblinded and a Group 1 Analysis was conducted. The Group 1 Analysis included PK, efficacy (primarily Hb response and subject reported outcome [PRO] measure endpoints), and safety data analysis to inform the dose selection and the final definition of PRO measure endpoints.
- Group 2 includes 212 randomized subjects, beginning with subject #63. Group 2 were randomized 1:1:1 to voxelotor 900 mg or 1500 mg or to placebo. Data from 94 subjects from Group 2 were unblinded to better inform the dose selection (termed Group 2a). Thus, data from a total of 156 subjects were unblinded and analyzed. The combined data from these 156 subjects (Groups 1 and 2a) and the remaining 118 subjects in Group 2 (termed Group 2b) that were not unblinded will provide an overall understanding of the efficacy and safety of voxelotor. In addition, demographic, baseline characteristics, key efficacy data, and key trial conduct parameters, e.g., percentage with missing Hb assessment at Week 24, from the 118 subjects in Group 2b will be analyzed for cohort comparability with Group 1 and Group 2a.
- As of the clinical data cutoff date of 31 October 2018 for the primary data analysis, all subjects enrolled on GBT440-031 will have reached a minimum study follow up of 24 weeks except for those who discontinued from the study prematurely.

This document describes the statistical methods and analysis outputs to be used in the summary and analysis of Group 1 and Group 2 data from Protocol GBT440-031 as well as the analysis of data from subjects in Group 2b. This statistical analysis plan (SAP) will be finalized prior to unblinding the Group 2b data. Where applicable, this SAP (version 5.0) supersedes the analysis plan discussion in Protocol Amendment 4.

Population pharmacokinetic (PK) analyses will be described in a separate document. Descriptive statistics for healthcare utilization are outside the scope of the SAP and will be summarized in a separate report.

2.1. Study Overview

This study is a randomized, placebo-controlled, double blind, parallel group, multicenter Phase III study, evaluating the safety and efficacy of voxelotor at 1500 mg and 900 mg dose level. Subjects meeting enrollment criteria were randomized in a 1:1:1 ratio to receive a daily dose of voxelotor 1500 mg, voxelotor 900 mg or placebo. The treatment duration was at minimum 12 weeks and may continue to a maximum of 72 weeks, with a key study endpoint of 24 weeks for the primary analysis of efficacy. The study will continue until all randomized subjects have reached Week 72 or discontinue from study early.

The study population includes SCD subjects with HbSS, HbSC, HbSβthalassemia, or other sickle cell syndrome variants. Subjects with 2 sickle hemoglobin genes (HbSS) or with compound heterozygosity for sickle Hb gene and beta thalassemia with no β globin expression (β0 thal) thalassemia (HbS β0 thal) are the SCD genotypes with most severe hemolysis and clinical symptoms. A history of at least one VOC in the past 12 months is required for enrollment. Subjects are also required to have Hb levels ≤10.5 g/dL and ≥5.5 g/dL.

SCD symptoms extend from infancy to adulthood. The population of this study includes adult and adolescent subjects (12 to 65 years).

Adolescent Subjects:

The study was to enroll only adult subjects initially. Adolescent subjects (ages 12 to <18 years) would be included in enrollment/randomization when:

1. Single dose PK data and modeling from Study GBT440-007 (pediatric subjects, 12-17 years of age) were available to confirm the appropriate dose for adolescent subjects, and
2. The DSMB had reviewed the safety data from at least 18 adults enrolled in this study of which at least 6 adults have received 1500 mg voxelotor for at least 4 weeks to confirm acceptable safety and tolerability before adolescents can be enrolled.

At the time that these criteria were met, adolescents would begin to enroll (as early as Group 1); a minimum of 50 adolescents would be included in the primary analysis of the study.

2.2. Study Measurements and Visit Schedule

Please refer to study protocol amendment 4 Appendix I for schedule of assessments.

3. OBJECTIVES

Primary Objective:

The primary objective is to assess the effect of voxelotor as measured by improvement in hemoglobin, compared to placebo.

Secondary Objectives:

The secondary objectives include the following:

- To assess the effects of voxelotor as compared to placebo on clinical measures of hemolysis, including unconjugated bilirubin, absolute reticulocyte, recticulocyte %, and LDH.
- To assess the effects of voxelotor as compared to placebo on long term Vaso-Occlusive Crisis (VOC).

Exploratory Objectives:

The exploratory objectives are to evaluate the effects of voxelotor compared to placebo on the following:

- Sickle Cell Disease Severity Measure (SCDSM),
- EuroQol EQ-5D-5L™ health questionnaire (EQ-5D-5L™),
- Clinical Global Impression Scale (CGI),
- Measures related to SCD pathophysiology and their utility as pharmacodynamic markers, e.g.,
  - Laboratory and clinical outcome measures including albumin creatinine ratio, scleral icterus, cholecystectomy and leg ulcers
  - Exploratory measures including RBC deformability and inflammatory markers
- School and/or work attendance and the use of opioid during the treatment period as recorded via eDiary,
- Time to first RBC transfusion and post baseline onset of VOC.
- Measures predictive of response to voxelotor.

Safety Objectives:

The safety objectives are to assess the safety of voxelotor based upon AEs, SAEs and SCD-related AEs, including VOC, acute chest syndrome (ACS) and Pneumonia, priapism, and osteonecrosis.

In addition, RBC transfusions, clinical laboratory tests, physical examinations, and other clinical measure events (e.g., discontinuations due to AEs, dose reductions) will also be evaluated.

Pharmacokinetic Objective:

The PK objective is to further assess the PK profile of voxelotor as evaluated by population PK analysis.

4. DEFINITIONS AND TERMINOLOGY

Study Drug

The term study drug refers to either voxelotor or placebo.

Baseline Value

Baseline measurements for efficacy and safety assessments will be the average of pre-treatment values (e.g., Screening and Day 1 pre-treatment). For PRO endpoints specific to SCD, e.g. TSS, the Baseline value is the average of the non-missing scores during the 28 to 35-day Screening period.

Day 1

Day 1 is the date of randomization.

Study Day

Study Day is defined relative to the date of randomization, i.e., Day 1.

For study assessments or events that occur on or after the date of randomization, the study day of an assessment/event is calculated as:

Study Day = event date – Day 1 date + 1.

For pre-randomization events, the study day is calculated as:

Study Day = event date – Day 1 date.

Study Visit

Study Visit is the nominal visit as recorded on the CRF.

Treatment Day

Treatment Day is defined relative to the date of initiation of study drug. This definition is essential when subjects are not dosed at Study Day 1, i.e. sometime after the date of randomization. Treatment day of an event that occurs on or after start date of dosing is calculated as:

Treatment Day = Event date – Start Date of Dosing + 1.

Extent of Exposure to Study Drug

Extent of exposure to study drug is defined as the number of weeks from initiation of study drug to the end of study drug treatment. Extent of exposure is calculated as follows:

$$\frac{(End\ of\ Treatment\ Date - Start\ Date\ of\ Dosing + 1)}{7},$$

Actual Exposure to Study Drug

Actual exposure to study drug is defined as the number of weeks from initiation of study drug to the last date of dosing of study drug which excludes days where treatment was entirely missed or intermittently stopped as recorded in the CRF. Duration of study drug exposure is calculated as follows:

$$\frac{\sum_{i=1}^{n}[End\ Date\ of\ Dose_i - Start\ Date\ of\ Dose_i + 1] \times I_{Dose_i}}{7},$$

where n is the number of dose modifications during the study and

$$I_{Dose_i} = \begin{cases} 0, if\ treatment\ dose\ i = 0\ mg \\ 1, if\ treatment\ dose\ i \neq 0\ mg \end{cases}.$$

Change from Baseline

Change from baseline for a given endpoint is defined as the Study Day value minus the Baseline value.

Hemoglobin Response at Week 24

Hemoglobin (Hb) response is based on the difference between the average value of Hb levels at Week 20 (Hb20) and Week 24 (Hb24) and baseline Hb level (HbB). A subject is considered to be a Hb responder if [mean(Hb20, Hb24) – HbB] > 1 g/dL. If Hb20 or Hb24 is missing, then the calculation will use the non-missing Hb level. Regardless of calculated difference, subjects will be classified as a non-responder if any of the non-responder criteria in Section 6.3.5.1 are met.

Hemoglobin Worsening at Week 24

- Severe anemic episode - worst Hb between weeks 12 and 24 inclusive is < 5.5 g/dL
- Acute anemic episode - worst Hb between weeks 12 and 24 inclusive, is >=5.5 g/dL and < 7 g/dL

Rate of Opioid Use During Treatment Period

The rate of opioid use is calculated as the number of days opioids were taken for SCD symptom management (as recorded in the eDiary) divided by the number of days with non-missing eDiary data from date of randomization to date of last dose.

Total Symptom Score (TSS)

For each subject, the TSS will be computed as follows: The Baseline TSS is the average of the scores during the 28 to 35-day Screening period. Similarly, post randomization when there is at least 75% compliance during a 4-week period, the TSS is the average score for each 4-week period. The 4-week periods are Weeks 1-4 (Study Day 1-28), Weeks 5-8 (Study Day 29-56), and Weeks 9-12 (Study Day 57-84) and follows similarly for subjects whose involvement exceeds 12 weeks up to Week 24. If there is a delay in initiating study treatment, all TSS data prior to administering treatment will be included with the Screening period data. All TSS data post dose through Study Day 28 will constitute Weeks 1-4. If missing data in a 4-week period is due to lack of compliance or subject dropout, the TSS will be set to missing for the 4-week period. Missing data due to VOC, VOC hospitalization or RBC transfusion will be imputed as described

in Section 6.3.5. Compliance of at least 60% during each 4-week period will also be examined in a sensitivity analysis for TSS.

TSS_{100} is TSS rescaled from a 27-point scale to 100-point scale. Algebraically, this is accomplished as follows:

$$TSS_{100} = TSS \times \frac{100}{27}.$$

Clinical Global Impression of Change

The Clinical Global Impression of Change (CGIC) is a 7-point scale that requires study medical personnel to assess clinically meaningful change in a participant's sickle cell disease. The rating scale is as follows:

- Very much improved
- Moderately improved
- Minimally improved
- No change
- Minimally worse
- Moderately worse
- Very much worse

CGIC is assessed at Week 24, Week 48, End of Treatment (EOT), and End of Study (EOS).

Incidences of VOC, RBC Transfusion, ACS or Pneumonia On Study

Cumulative incidences of each named event is defined as the number of events from date of randomization to end of study, inclusive.

Time (in weeks) to First VOC

Time to first VOC during the study is defined as

(Date of First VOC On Study – Date of Randomizaton + 1) / 7.

Subjects who do not have a VOC will be censored at the end of study.

Time (in weeks) to First RBC Transfusions

Time to first RBC transfusions during the study is defined as

(Date of First RBC transfusion On Study – Date of Randomization + 1) / 7.

Subjects who do not have an RBC transfusion will be censored at the end of study.

Time (in weeks) to First ACS or Pneumonia

Time to first ACS or Pneumonia during the study is defined as

(Date of First ACS or Pneumonia On Study – Date of Randomization + 1) / 7.

Subjects who do not have an ACS or pneumonia will be censored at the end of study.

Adverse Event

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product during the course of a clinical investigation. For greater details, refer to Protocol Section 9.1.1.

All adverse events will be recorded on the Adverse Event CRF.

For this study's definition of a Serious Adverse Event (SAE), please refer to Protocol Section 9.1.2.

Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges on or after initiation of study drug (having been absent pre-treatment), or an AE that existed pre-treatment and worsened on treatment (relative to the pre-treatment state) through 28 days after study drug discontinuation.

Treatment-emergent Laboratory Abnormalities

A Treatment-emergent Laboratory Abnormality is defined as any post-baseline laboratory assessment that emerges on or after initiation of study drug through 28 days after study drug discontinuation, which demonstrates an increase of 1 grade or more from the baseline toxicity value. If the baseline value is missing, any graded abnormality (grade 1 or higher) that occurs following initiation of study drug through 28 days after study drug discontinuation is deemed treatment-emergent.

Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of study drug. This definition includes medications started prior to the initiation of study drug but continue concurrently with study drug.

Prior Medications

Prior medications are those medications taken prior to the initiation of study drug.

5. STUDY ENDPOINTS

Primary Endpoint:

The primary efficacy measure is Hb response at Week 24, as defined in Section 4.

Secondary Endpoints:

The secondary efficacy endpoints are as follows:

- Change from baseline in hemoglobin at Week 24
- Change and percent change from baseline in hemolysis measures, including unconjugated bilirubin, absolute reticulocyte, reticulocytes %, and LDH
- Annualized incidence rate of VOC

Exploratory Endpoints:

- Change from baseline in hemoglobin at Week 48 and Week 72
- Change and percent change from baseline in hemolysis measures: including unconjugated bilirubin, absolute reticulocytes, reticulocytes %, and LDH, at Week 48 and Week 72
- Time to first VOC
- Time to first ACS or pneumonia
- Time to first RBC transfusion
- Rate of opioid use as recorded in the eDiary
- Sickle Cell Disease Severity Measure (SCDSM)
- EuroQol EQ-5D-5L™ health questionnaire (EQ-5D-5L™)
- Clinical Global Impression Scale (CGI)
- School and/or work attendance as recorded via eDiary

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. Sample Size and Power

The sample size for the primary analysis of the study, including both Groups 1 and 2, is 274 randomized subjects. All randomized subjects will be included in the efficacy analysis.

For the primary analysis of hemoglobin response rate comparing voxelotor 1500 mg to placebo, assuming a 10% Hb response rate in placebo, the study with approximately 90 subjects per treatment group will have >95% power to detect a targeted difference of 30%, using Fisher's exact test with a two-sided alpha of 0.0481.

6.2. Randomization and Unblinding

Randomization was carried out centrally through an IXRS. Permuted blocks within randomization strata were used. At the time of randomization, subjects were stratified for hydroxyurea (HU) use (yes/no), geographic region (North America, Europe, Other), and age (adolescent, 12 to <18 years, and adults, 18 to 65 years).

This study is designed as a double-blinded study. The voxelotor and placebo capsules or tablets were matched for shape, size, and color.

To facilitate the Group 1 and 2a Analyses, certain Sponsor representatives and Sponsor designees were unblinded to treatment assignments prior to and during the analysis (including the biostatistics contract research organization [CRO], Sponsor Biostatistics and Programming staff, and external groups for bioanalytical PK/PD). However, except for those noted above, the rest of the Sponsor study team, including all study team members who have direct interactions with study sites, was not unblinded to individual treatment assignment. No site staff or study subjects were unblinded to randomization assignment.

6.3. Handling of Data

6.3.1. Strata

Unless otherwise specified, analysis of data from subjects in Groups 1 and 2 combined will be adjusted for the randomization stratification factors.

For Group 2b analysis, due to the small sample size of n=118, adjustment for the randomization stratification factors will be made only for a single stratification factor. The stratification factor that will be used in the Group 2b analysis is HU use at baseline.

6.3.2. Examination of Subject Subsets

Subgroups defined by subject age group, (adolescent, 12 to <18 years; and adults, 18 to 65 years), geographic region (North America, Europe, Other), baseline HU use (yes, no), baseline VOC history (1, >1) will be analyzed to evaluate the internal consistency of the study outcomes. Subgroups defined by baseline Hb level will also be explored.

In addition, comparability of study cohorts (e.g., Group 1, Group 2a, Group 1 & 2a, and Group 2b) will be assessed. Specifically, descriptive statistics will be presented for each study cohort regarding the following:

- Demographics
- Baseline disease characteristics
- Subject disposition by study visit
- Rates of missing Hb assessment at Week 24

Hb response rate and Hb change from baseline in voxelotor treatment groups compared to placebo will also be summarized by study cohort.

6.3.3. Multiple Testing and Comparisons

A fixed sequence hierarchical test procedure will be used to formally evaluate voxelotor 1500 mg and 900 mg dose groups in comparison to placebo. The analysis will be based on data from the ITT population (i.e., all randomized subjects).

Interim Efficacy Analysis

Two interim analyses (IA) were to be performed to inform voxelotor dose selection. The first IA was performed with Group 1 data (n=62), followed by the second IA with the combined Groups 1 and 2a (n=156). The primary analysis will be performed based on data from all randomized subjects in Group 1 and Group 2 (n=274). A Lan-DeMets alpha spending function with the O'Brien-Fleming boundary is used to determine the significance level for each IA and the primary analysis, to maintain an overall type I error rate of 5% (two-sided), resulting in the following:

Analysis	Significance Level (two-sided)
IA #1 (n = 62)	0.000005
IA #2 (n = 156)	0.0059
Primary Analysis (n = 274)	0.0481

PASS Software (version 11) was used to calculate the alpha spending for each analysis (two-sample proportion).

Primary Efficacy Analysis

The first hypothesis testing will be to compare Hb response rate in voxelotor 1500 mg vs placebo. The test hypotheses are as follows:

$H_0: p_v = p_c$ vs $H_a: p_v \neq p_c$

where p_v is the Hb response rate in voxelotor 1500 mg group and p_c is the Hb response rate in the placebo group.

The exact Cochran-Mantel-Haenszel (CMH) general association test, stratified by baseline HU use, age and geographic region, will be used for this analysis.

Secondary Efficacy Analyses

If the null hypothesis in the primary efficacy analysis is rejected at a two-sided significance level of 0.0481, the following hierarchically ordered statistical hypotheses will be tested in the order specified below, until the first non-rejection.

1. Change from baseline at Week 24 in Hb: voxelotor 1500 mg vs Placebo
2. Percent change from baseline at Week 24 in unconjugated bilirubin: voxelotor 1500 mg vs. Placebo
3. Percent change from baseline at Week 24 in reticulocyte %: voxelotor 1500 mg vs Placebo
4. Percent change from baseline at Week 24 in LDH: voxelotor 1500 mg vs Placebo
5. Hb response rate at Week 24 in Hb: voxelotor 900 mg vs Placebo
6. Change from baseline at Week 24 in Hb: voxelotor 900 mg vs Placebo
7. Percent change from baseline at Week 24 in unconjugated bilirubin: voxelotor 900 mg vs Placebo
8. Percent change from baseline at Week 24 in reticulocyte %: voxelotor 900 mg vs Placebo
9. Percent change from baseline at Week 24 in LDH: voxelotor 900 mg vs Placebo

6.3.4. Visit Windows

The blinded study period begins with the date of randomization, which is denoted in the protocol as Study Day 1. The conventions outlined below will be used to associate data measures, according to the study day corresponding to the date the data was collected, to an analysis visit window based on nominal (i.e., planned) visits, using the measure's study day relative to Day 1. Data collected before Study Day 1 will be considered screening information. Target study days, protocol acceptable ranges (per protocol) of study days for each scheduled assessment, and the analysis visit windows defined for each nominal visit day are shown in Tables 1 and 2.

If multiple assessments occur within a visit window, then the average of those assessments will be used for summarization and analysis.

Summarizations and analyses will utilize scheduled assessments and unscheduled assessments within a particular nominal window. Only central laboratory assessments will be included in summarizations and analyses of laboratory analytes.

Visit windows will be defined separately for non-PRO and PRO measures. PRO measures include ePRO Screening, ePRO SCD Severity Measure (SCDSM), eDiary data, EQ-5D-5L™, and CGI.

Table 1: Nominal Analysis Visit Windows for Non-PRO Measures

Nominal Visit Time	Target Study Day	Per Protocol Study Day Range	Study Day Range for Statistical Analysis*
Screening	-	[-35, -1]	[-35, -1]
Day 1	1	[-1, 1]	[-1, 1]
Week 2	14	[12, 16]	[2, 21]
Week 4	28	[26, 30]	[22, 35]
Week 6	42	[40, 44]	[36, 49]
Week 8	56	[54, 58]	[50, 70]
Week 12	84	[79, 89]	[71, 98]
Week 16	112	[107, 117]	[99, 126]
Week 20	140	[135, 145]	[127, 154]
Week 24	168	[163, 173]	[155, 210]
Week 36	252	[245, 259]	[211, 294]
Week 48	336	[329, 343]	[295, 378]
Week 60	420	[413, 427]	[379, 462]
Week 72	504	[497, 511]	[463, 545]

* Baseline is defined as the average of assessments on or prior the Study Day 1.

Table 2: Nominal Analysis Visit Windows for PRO Measures+

Nominal Visit Time	Study Day Range for Statistical Analysis*
Screening	[-35, -1]
Week 4	[1, 28]
Week 8	[29, 56]
Week 12	[57, 84]
Week 16	[85, 112]
Week 20	[113, 140]
Week 24	[141, 168]
Week 36	[169, 252]
Week 48	[253, 336]
Week 60	[337, 420]
Week 72	[421, 504]

* SCDSM scores on Study Days < -35 and Study Days > 168 will be excluded from SCDSM analyses

+ Notes:

(1) ePRO SCDSM is measured every day from the first day of Screening to Week 24 post randomization.

(2) EQ-5D-5L™ is administered at Day 1, Week 12 and then every 12 weeks while the subject remains on study. The final assessment of EQ-5D-5L™ will occur 4 weeks after the last dose of study drug. For the assessment of EQ-5D-5L™, Day 1 is defined as Baseline.

(3) The eDiary is triggered from Day 1 through EOS.

6.3.5. Imputation of Missing Data for Evaluation of Efficacy

Guidelines regarding how missing data will be handled for each efficacy endpoint are described below.

6.3.5.1. Hemoglobin Responder

- If Hb assessment is missed at both Week 20 and Week 24 due to dropout, VOC, or VOC hospitalization: Subject will be treated as a non-responder. If Hb at one of the two time points is non-missing, Hb response assessment will be based on the non-missing Hb value.
- Initiation of HU post randomization and prior to Week 24: Subject will be treated as a non-responder.

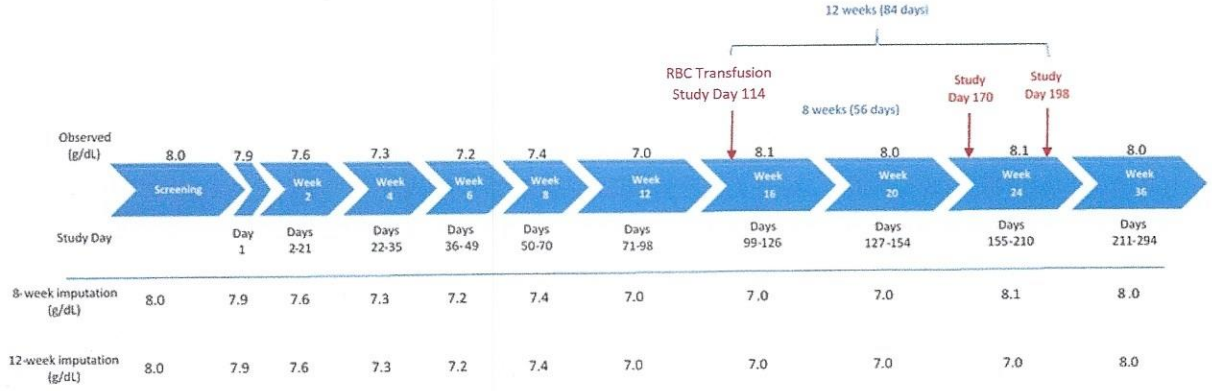
- RBC transfusions: A participant who receives a transfusion due to anemia within 8 weeks (12 weeks for sensitivity analysis) of the Week 24 Hb assessment will be deemed a non-responder. For subjects receiving transfusion due to reasons other than anemia within 8 weeks (12 weeks for sensitivity analysis) of the Week 24 Hb assessment, Week 24 Hb will be imputed with the last Hb assessment prior to the transfusion.

  Example: In Figure 1, an RBC transfusion due to anemia occurred at Day 114. If the Week 24 Hb assessment occurs before Day 170 then the participant will be deemed a non-responder; otherwise the Week 24 Hb measure will then be compared to Baseline to determine whether the participant meets the definition of responder (i.e. 8.1 – 7.95 = 0.15, which is classified as a non-responder). If the RBC transfusion is not due to anemia, then the Hb assessment prior to Day 114 (i.e., the Week 12 assessment, which is 7.0 g/dL) will be used for imputation of Hb for assessments occurring from Study Day 114 to Study Day 170 (8-week imputation) or to Study Day 198 (12-week imputation). The Week 24 Hb measure will then be compared to Baseline to determine whether the participant meets the definition of responder.

6.3.5.2. Hemolysis Measures Change from Baseline and hemolysis reduction

- Missing data due to subject dropout: For the primary method of analysis of this endpoint (mixed effect model for repeated measures [MMRM]), missing at random (MAR) will be assumed and no imputation will occur.
- Subjects initiating HU post randomization will be discontinued from the study. As such, only assessments prior to HU initiation will be used in this analysis.
- Missing Week 24 hemolysis data due to VOC or VOC hospitalization: For the primary method of analysis of hemolysis measures (MMRM), missing at random (MAR) will be assumed and no imputation will occur. For sensitivity analysis, the imputation rule for missed assessments due to VOC or VOC hospitalization will be assigned the hemolysis measurement from the last assessment (Table 1) occurring prior to commencement of VOC or hospitalization for VOC (including Screening and Day 1).
- RBC transfusions: Regardless of whether data are missing, post transfusion hemolysis lab results will be imputed by assigning the hemolysis measurement of the last assessment prior to transfusion (including Screening and Day 1). All hemolysis lab results starting on the transfusion date and ending 8 weeks after are imputed for the MMRM analysis of hemolysis measures and the assessment of hemolysis reduction at Week 24. All hemolysis lab results starting on the transfusion date and ending 12 weeks after are imputed for the related sensitivity analysis. See Figure 1. The imputation for Hb is similarly applied to all measures of hemolysis for the change from baseline analyses.

Figure 1: RBC Transfusion Imputation for Hb Assessment



6.3.5.3. Total Symptom Score (PRO measure)

- Missing data due to missed diary entries or subject dropout: If a subject has 7 or more missed diary entries unrelated to VOC or hospitalization due to VOC in a 4-week period, the TSS will be set to missing for that period. Specifically, determine the rate of compliance for each 4-week interval. If a 4-week interval has a compliance rate of less than 75% (or < 60% sensitivity), then the interval summary value is set to missing. Otherwise, the mean of the observations within the interval is used as the summary value.
- Subjects initiating HU post randomization will be discontinued from the study. As such, only assessments prior to HU initiation will be used in this analysis.
- Missing data due to VOC or VOC hospitalization: Subject will be assigned his/her worst TSS score prior to the commencement of the VOC or VOC hospitalization. Example: Assume a subject was hospitalized from Day 35 – Day 39 and did not respond to the SCDSM questionnaire during this period. For Days 35 – 39, the worst TSS score for the subject up to Day 35 will be used for each day PRO data are missing.
- RBC transfusions: Regardless of whether data are missing, post transfusion data will be imputed for the 8-week period (12-week period for sensitivity analysis) after the transfusion. The TSS in the last 4-week period with a non-missing score prior to transfusion (including the Screening period) will be substituted for each day during this 8-week period post transfusion (12-week period for sensitivity analysis). Specifically, determine the TSS for the last 4-week interval prior to transfusion which meets the compliance threshold. Use this value to impute 8 weeks (or 12 weeks for sensitivity analysis) post transfusion.

The PRO imputation rules have a hierarchy in situations where there are missing data and RBC transfusions have been administered during participation in the study. The ordering of imputation rules is as follows:

1. Impute missing TSS data due to VOC and/or VOC hospitalization as specified above.
2. Apply imputation rule based on rate of compliance for each 4-week interval as specified above.
3. Impute TSS data potentially affected by RBC transfusion as specified above.
4. Apply imputation rule based on rate of compliance once more for each 4-week interval as specified above.

If a subject no longer wishes to participate in the study and withdraws consent or if a subject initiates HU post randomization (resulting in discontinuation from the study), the end of study date is the last day in which imputation may occur, i.e. imputation will not surpass the end of study day.

Refer to Section 6.3.6 for details of imputing missing dates. Unless otherwise specified, no other missing data imputation is planned.

Example: For a given subject, assume an RBC transfusion occurs on Study Day 35. The largest TSS from the Screening Period (30 days) and Weeks 1-4 (28 days) will be used to impute the TSS on Day 35 through Day 91 (8 weeks). Based upon Figure 2, the Screening Period had an average TSS of 17 and Weeks 1-4 had 21.

Assume the average TSS prior to RBC transfusion for Days 29 -34 was 20. The average TSS for Weeks 5-8 is computed as follows:

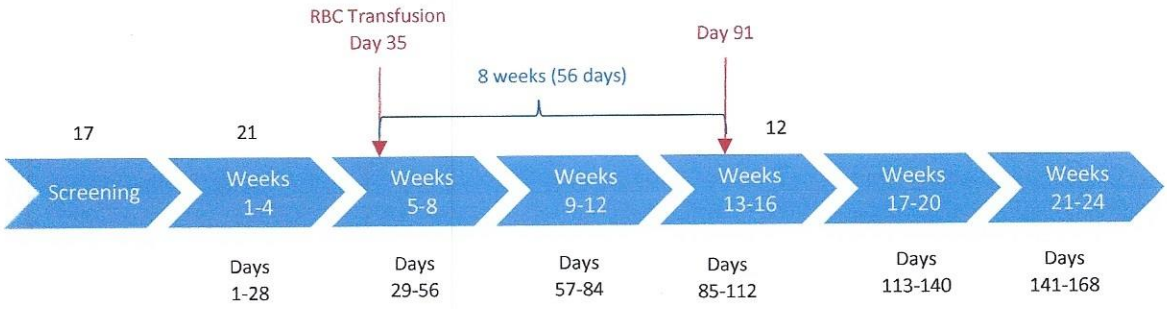
$$\frac{[(34-29+1)20+(56-35+1)21]}{(56-29+1)}=20.79$$

The average TSS for Weeks 9-12 is 21.

After transfusion, on Days 91-112, assume the average TSS was 12. The average TSS for Weeks 13-16 is computed as follows:

$$\frac{[(91-85+1)21+(112-92+1)12]}{(112-85+1)}=14.25$$

Figure 2: RBC Transfusion Imputation for TSS Score



6.3.6. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed as follows.

For concomitant medications, the case report form permits the start date to have an unknown day and/or month.

6.3.6.1. Start Dates for Concomitant Medications

- For missing start day only – Day will be imputed as the first day of the month (i.e., 1) with the following exception: If the partial date falls in the same month and year as the treatment start date then the concomitant medication start date will be imputed as the treatment start date.
- For missing start day and month – Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: If the partial date falls in the same year as the treatment start date then the concomitant medication start date will be imputed as the treatment start date.

6.3.6.2. Stop Dates for Concomitant Medications

- For missing stop day only – Day only will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).
- For missing stop day and month – Day and month will be imputed as the last day of the year (i.e., 31 December).

For adverse events, the case report form permits the date to have an unknown day. If day is missing, then a question on the case report form asks whether the event started prior to the first dose.

6.3.6.3. Start Dates for Adverse Events where the event occurs prior to the first dose

- For missing start day only – Day will be imputed as the first day of the month (i.e., 1) with the following exception: If the partial date falls in the same month and year as the treatment start date then the adverse event start date will be imputed as the day prior to the treatment start date.

6.3.6.4. Start Dates for Adverse Events where the event is not prior to the first dose

- For missing start day only – If the partial date falls in the same month and year as the treatment start date then the adverse event start date will be imputed as the treatment start date. Otherwise, the day will be imputed as the first day of the month (i.e., 1) as long as the imputed date does not occur before the treatment start date.

6.3.6.5. Stop Dates for Adverse Events

- For missing stop day only – Day only will be imputed as the last day of the month (i.e., 28, 29, 30, or 31).

For study drug exposure, the case report form permits the date to have an unknown day. However, due to daily dosing, partial dates will not be imputed.

Any partial dates will be displayed in data listings without imputation of missing days and/or months (e.g., JAN2017, 2015).

6.4. TIMING OF ANALYSES

When all Group 2 randomized subjects have reached 24 weeks of study participation or discontinues from study early, and once all data have been cleaned and database frozen for analysis, the safety and efficacy analysis of GBT440-031 will be performed according to this SAP.

7. ANALYSIS POPULATIONS

7.1. Intent to Treat (ITT) Population

All subjects who were randomized in the study will be included in the ITT population. Subjects will be analyzed based upon the treatment group to which they were assigned at randomization. This is the primary population for efficacy analysis.

7.2. Modified Intent to Treat (mITT) Population

All subjects who are randomized to a treatment group and receive at least one dose of study medication will be included in the Modified Intent to Treat Population. Subjects will be analyzed based upon the treatment group to which they were assigned at randomization. Selected efficacy endpoints, e.g., Hb response rate, may be analyzed based on the mITT population as supportive analysis.

7.3. Safety Population

All subjects who receive at least one dose of study medication will be included in the Safety Population. Subjects will be analyzed based upon study treatment they received. This is the primary population for safety analyses.

8. STATISTICAL METHODS

Statistical programming and analyses will be performed using established statistical methods. Information related to blinding (and unblinding) during the conduct of the study is provided in Section 6.2 and in Protocol Section 8.3. All statistical tests will be conducted at a two-sided significance (alpha) level of 0.05 unless otherwise stated.

The study data will be reported using tables, figures, and data listings. Descriptive statistical methods will be used to summarize the data from this study. Continuous variables will be descriptively summarized using number of subjects (n), mean, standard deviation (SD), coefficient of variation (CV%, as appropriate), median, minimum, maximum, inter-quartile range (IQR), and, geometric mean as appropriate. Categorical variables will be descriptively summarized by presenting the number (frequency) and percentage in each category. Kaplan-Meier or cumulative incidence curves will be used to present time to event or recurrent event data, as appropriate. Data for subjects who provide diary data but discontinue treatment and continue in the study will be included in the analysis. Hypothesis testing will be performed for the primary and select endpoints as specified in Section 6.3.3.

Unless otherwise noted, data listings will be sorted by treatment group, subject number, and then, where applicable, by visit or assessment date within each subject number.

The statistical analyses will be conducted with the SAS® System version 9.4 or higher. All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical analysis outputs. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

8.1. Subject Disposition, Demographic and Baseline Characteristics

Subject disposition will be presented for all subjects in the ITT population. The number of subjects who completed the study and discontinued from the study will be provided. The reasons for early discontinuation at any point also will be presented by treatment group. Additionally, the number of weeks on study and study drug will be summarized for all treated subjects.

Demographic data and baseline characteristics, including age, gender, race, ethnicity, VOC history, Baseline Hb, Baseline SCDSM TSS, Baseline absolute reticulocyte, and Baseline reticulocytes %, will be summarized using descriptive statistics. This information will be reviewed for baseline differences, but no statistical testing will be performed.

Medical/surgical history and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 for the entire period of the study. Medical/surgical history and adverse events will be summarized in tables and may be presented in data listings.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (version WHO-DD01Sep2016) for the entire period of the study. Prior and concomitant medications will be summarized in tables and may be presented in data listings.

8.2. Efficacy Analysis

8.2.1. Primary Endpoint

8.2.1.1. Primary Analysis of Hemoglobin Response

For the primary analysis of Hb response, individual subject data through Week 24 will be included.

The Hb response rate will be analyzed using an exact Cochran-Mantel-Haenszel (CMH) general association test with imputation rules outlined in Section 6.3.5. Each voxelotor dose group (900 mg and 1500 mg) will be compared to placebo while stratifying for the randomization stratification factor of HU use, age group and geographic region. Sample SAS code for the exact CMH general association test will be similar to the following:

```
PROC LOGISTIC;
  CLASS treatment/PARAM=REF;
  FREQ count;
  MODEL response = treatment;
  STRATA stratum;
  EXACT treatment;
RUN;
```

8.2.1.2. Additional Analysis of Hb

Change from baseline in Hb over time up to Week 24 will be analyzed using a mixed effect for repeated measures (MMRM) model. The fixed effect terms include treatment, study visit, treatment by visit interaction, HU use at baseline, age group and geographic region. Baseline Hb will be a co-variate. Within-subject variability will be modeled using an unstructured covariance matrix. Missing data due to early drop out or missed visit will not be imputed for this analysis. Missing data to due to VOC, VOC hospitalization or RBC transfusion will be imputed, as described in Section 6.3.5.

Change from baseline in hemoglobin up to Week 48 and Week 72 will be analyzed similarly with available data as of the clinical cutoff date for the primary analysis.

The adjusted mean (lsmean) change from baseline in Hb at each visit, estimated from the MMRM model, with the estimated standard error and 95% confidence interval (CI), will be presented in tabular and graphic format. The difference in the adjusted means between treatment groups and the associated 95% CI of the difference will be provided.

Hb worsening will summarized using a shift table for each treatment group. Incidences of post-baseline Hb < 5.5 g/dL will be summarized by treatment group, as well as incidences of Hb change from baseline < -2 g/dL.

Proportion of subjects with Hb of ≥10 g/dL at Week 24 will be explored.

All analyses specified above will be based on data with imputation for RBC transfusion, VOC and VOC hospitalization, as applicable. The analysis of Hb response rate will also be repeated using observed data without imputation to assess the robustness of the data.

8.2.2. Secondary Endpoints

Unless otherwise specified, data will be analyzed with respect to Week 24. Data summaries beyond Week 24 will be tabulated.

8.2.2.1. Change from Baseline to Week 24 in Hemolysis Related Measures

Percent change from baseline over time up to Week 24 in unconjugated bilirubin, absolute reticulocyte, reticulocytes %, and LDH will be analyzed with a similar MMRM model and summarized in tabular and graphic format as for change from baseline to Week 24 in Hb.

In addition, the absolute and percent changes from Baseline to Week 24 in each hemolysis measure, including absolute reticulocyte, reticulocytes %, and unconjugated bilirubin will be presented descriptively via tabulation of descriptive statistics by treatment group.

If any of the laboratory measures reported are below the lower limit of quantitation or above the upper limit of quantitation, then the numerical limit will be used in the MMRM modeling and the tabulation of the descriptive statistics.

8.2.2.2. VOC up to Week 72

The number of VOC events will be modeled using a negative binomial model with the independent variable of treatment group and adjusted for the stratification factors used for randomization. Additional risk factors, including number of VOC occurrences during the 12 months prior to randomization, will also be explored.

The mean cumulative function of VOC events will be presented using recurrent events analysis methods.

Annualized incidence rate will be summarized for each treatment group.

These analyses will be repeated in a follow up analysis when all subject reaches 72 weeks of study participation or discontinues from the study early.

8.2.3. Exploratory Endpoints

8.2.3.1. Time to Event Analysis

Kaplan Meier methods will be used to summarize time-to-event endpoints, including time to first VOC, time to first ACS or pneumonia and time to first RBC transfusion. Event rates will be estimated at landmark time points, e.g., Week 12, Week 24, Week 48, as appropriate.

Rate of opioid use, and rate and reasons for RBC transfusion will be summarized descriptively by treatment group.

8.2.3.2. Patient-Reported Outcomes

PRO measures, including Sickle Cell Disease Severity Measure, EQ-5D-L heath questionnaire, Clinical Global Impression (CGI), will be summarized descriptively.

8.2.3.3. Proportion of School and/or Work Attendance Days

The proportion of school and/or work attendance days will be modeled via analysis of variance (ANOVA). The model will include fixed effect terms of treatment group and the randomization stratification factor HU use, age and geographic region. The proportion of subjects who were absent from school/and/or work, the frequency distribution of days absent from school and/or work, and the exposure adjusted incidence of absence from school and/or work will be tabulated by treatment group.

8.3. Safety

Safety analysis will be performed on all subjects as well as adolescents receiving at least one dose of study drug, with Groups 1 and 2 combined. All safety assessments, including AEs, clinical laboratory evaluations, vital signs, physical examinations, 12-lead ECG results, and echocardiograms will be summarized with descriptive statistics.

8.3.1. Summary of Exposure

Study drug administration will be summarized with number and percentage of subjects receiving from 1 to the maximum number of doses by treatment group. Similarly, the duration of treatment will be summarized with descriptive statistics.

8.3.2. Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary (version WHO-DD 01Sep2016). Concomitant medications will be summarized descriptively by treatment group.

8.3.3. Adverse Events

AEs will be mapped to system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1.

The total number and percentage of subjects with TEAEs will be presented by SOC and preferred term for each treatment group. TEAEs will be presented by severity. TEAEs will be tabulated presenting the SOC alphabetically and within each system the preferred term will be presented in decreasing order of the total number of voxelotor-treated subjects who experienced each TEAE. Treatment-related adverse events will be similarly presented.

The frequency of subjects who experience each TEAE or treatment-related AE will be determined as follows: A subject experiencing the same AE multiple times will only be counted once for the preferred term. Similarly, if a subject experiences multiple AEs within the same SOC, that subject will be counted only once for that system. If changes in the severity of an AE are recorded in the eCRF, only the most severe incidence of the AE will be counted. If a subject experiences multiple occurrences of a TEAE, only the related event or the worst severity

(analysis dependent), will be counted for each subject within each SOC or preferred term for the summaries of treatment-related AEs.

Missing onset dates will be imputed as previously outlined in Section 6.3.6 as required to determine treatment-emergent events. Should an event have a missing severity or relationship to study medication, then the severity or relationship, respectively, will be classified as missing for summary tabulation purposes.

Listings of AEs leading to discontinuation of the study, SAEs and deaths, if any, will be provided.

Annualized incidence rates of VOC, ACS and pneumonia, priapism, and osteonecrosis will be summarized by treatment group and severity grade.

8.3.4. Clinical Laboratory Assessments

All hematology and chemistry laboratory assessments were performed by a central laboratory. Laboratory data will be converted into System International (SI) units for the analysis.

The following protocol-specified clinical laboratory findings will be summarized using descriptive statistics by treatment group, without any imputation:

1. Hematology:
    a. Hemoglobin
    b. Neutrophils
    c. Platelets
    d. Absolute reticulocytes
    e. Reticulocyte %
    f. WBC
2. Chemistry:
    a. Alkaline phosphatase
    b. ALT
    c. AST
    d. Indirect bilirubin
    e. Potassium

Descriptive statistics will be presented for baseline, each evaluation post baseline, and change from baseline for each post baseline evaluation. If any of the clinical laboratory assessments are below the lower limit of quantitation or above the upper limit of quantitation, then the numerical limit will be used in the tabulation of the descriptive statistics.

Laboratory abnormalities will be graded via the Common Terminology Criteria for Adverse Event (CTCAE) version 4.0. The number and percentage of subjects experiencing treatment-emergent graded abnormalities will be summarized by treatment group. Laboratory abnormality shifts from baseline through Week 24 will be summarized by treatment group. Laboratory abnormality shifts of an increase of one grade or more from baseline will be presented in a data listing.

8.3.5. Vital Signs

Vital signs (oral temperature, respiratory rate, heart rate, and systolic/diastolic blood pressure) will be summarized using descriptive statistics for baseline, each study evaluation, and change from baseline for each post-baseline evaluation.

The average of each vital sign parameter collected at Screening and Day 1 (pre-dose) will be the baseline.

8.3.6. 12-lead Electrocardiograms

Twelve-lead electrocardiogram data (ventricular heart rate [HR] and conduction intervals [RR, PR, QRS, QT, and QTcF]) will be reported for subjects with clinically significant findings. These clinically significant ECG findings will be presented in listings.

9. PROTOCOL DEVIATIONS

Protocol deviations as assessed by the study team will be displayed in a data listing and sorted by treatment group, subject number, and then by date (where applicable) within each subject number. The type of deviation along with a description and any additional comments about the deviation will be listed.

10. CHANGES IN THE PLANNED ANALYSES

Additional analyses that are included in the clinical study report but are not mentioned in the SAP will be identified as such.

11. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects.
- Group headers: In the summary tables, the group headers will identify the summary group and the sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population due to missing data.
  - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations. The number of missing observations, if any, will be noted.
  - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation. The number of missing observations, if any, will be noted.
- Sorting: Listings will be sorted by treatment group, subject number, and (where applicable) then by date within each subject number. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of

rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.

- The presentation of numerical values will adhere to the following guidelines:
  - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
  - Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
  - Means will be reported to the same number of significant digits as the parameter.
  - Calculated percentages will be reported with no decimals.
- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HH:MM).

12. REFERENCES

1. Kenward, MG, and Roger, JH. (1997). Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. Biometrics, 53: 983–997.
2. Penman, AD, and Johnson, WD. (2008). A SAS program for calculating cumulative incidence of events (with confidence limits) and number at risk at specified time intervals with partially censored data. Computer Methods and Programs in Biomedicine, 89: 50-55.
3. Powers, JH, Patrick DL, Walton, MK, et al. (2017). Clinician-Reported Outcome Assessments of Treatment Benefit: Report of the ISPOR Clinical Outcome Assessment Emerging Good Practices Task Force. Value in Health, 20: 2-14.

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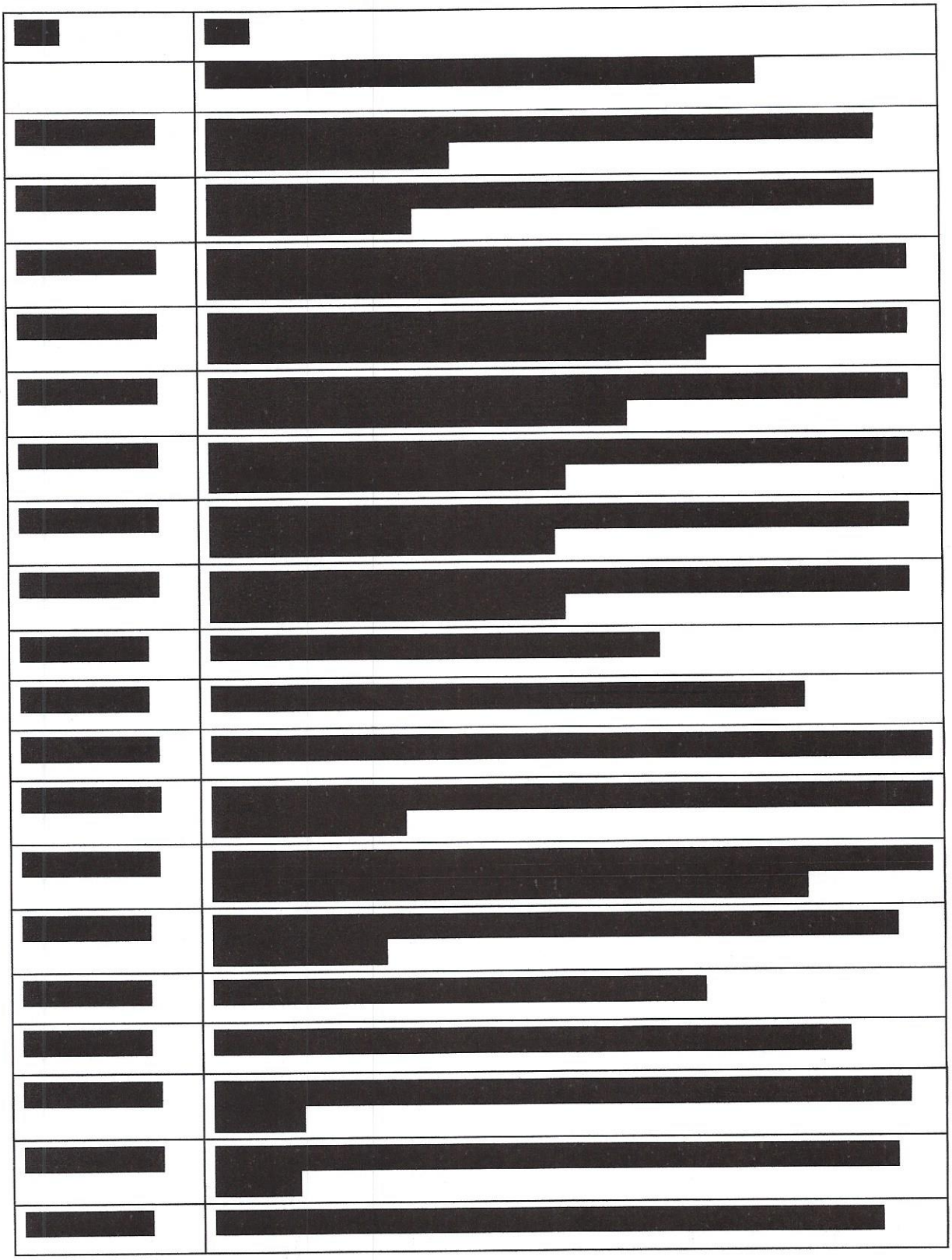

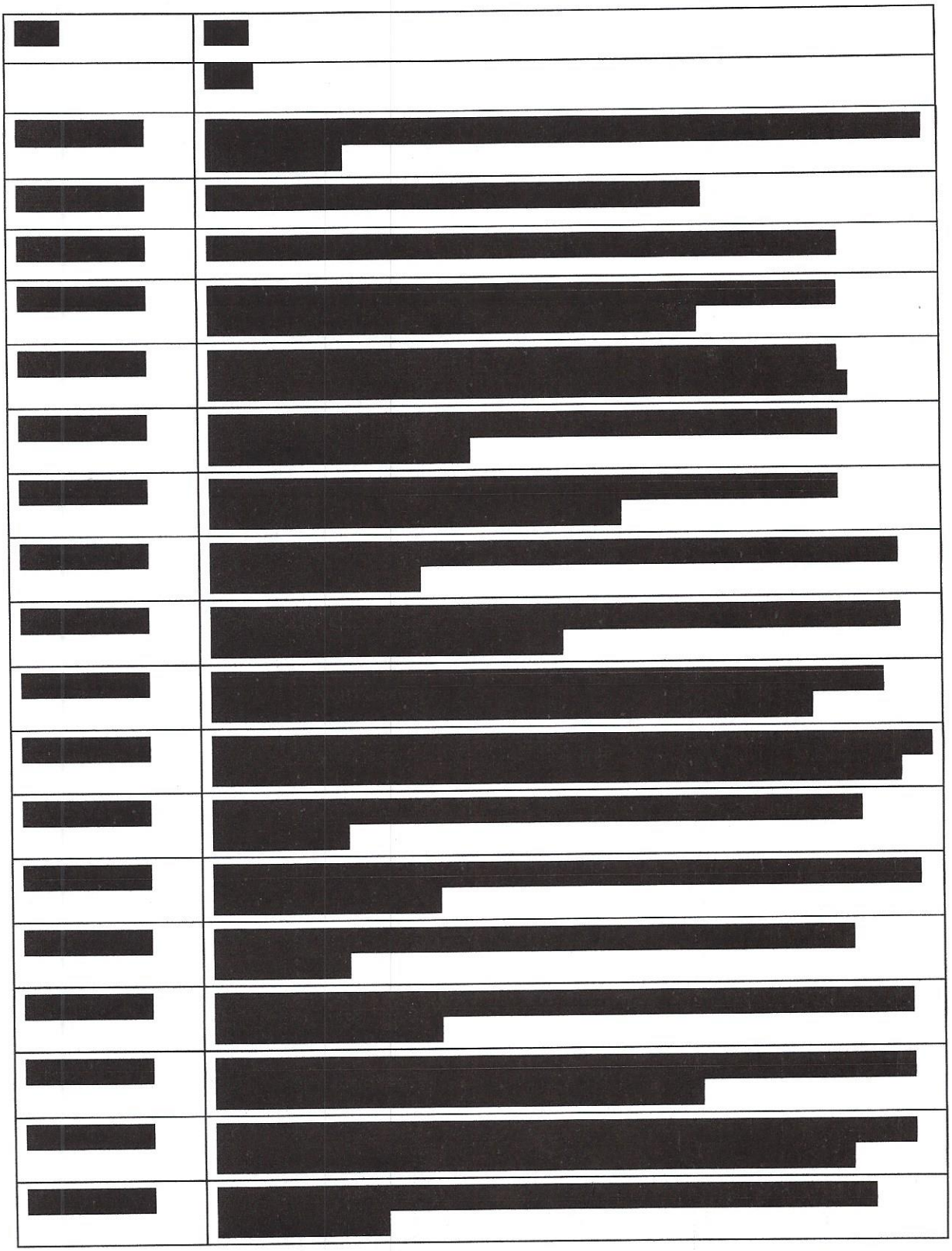

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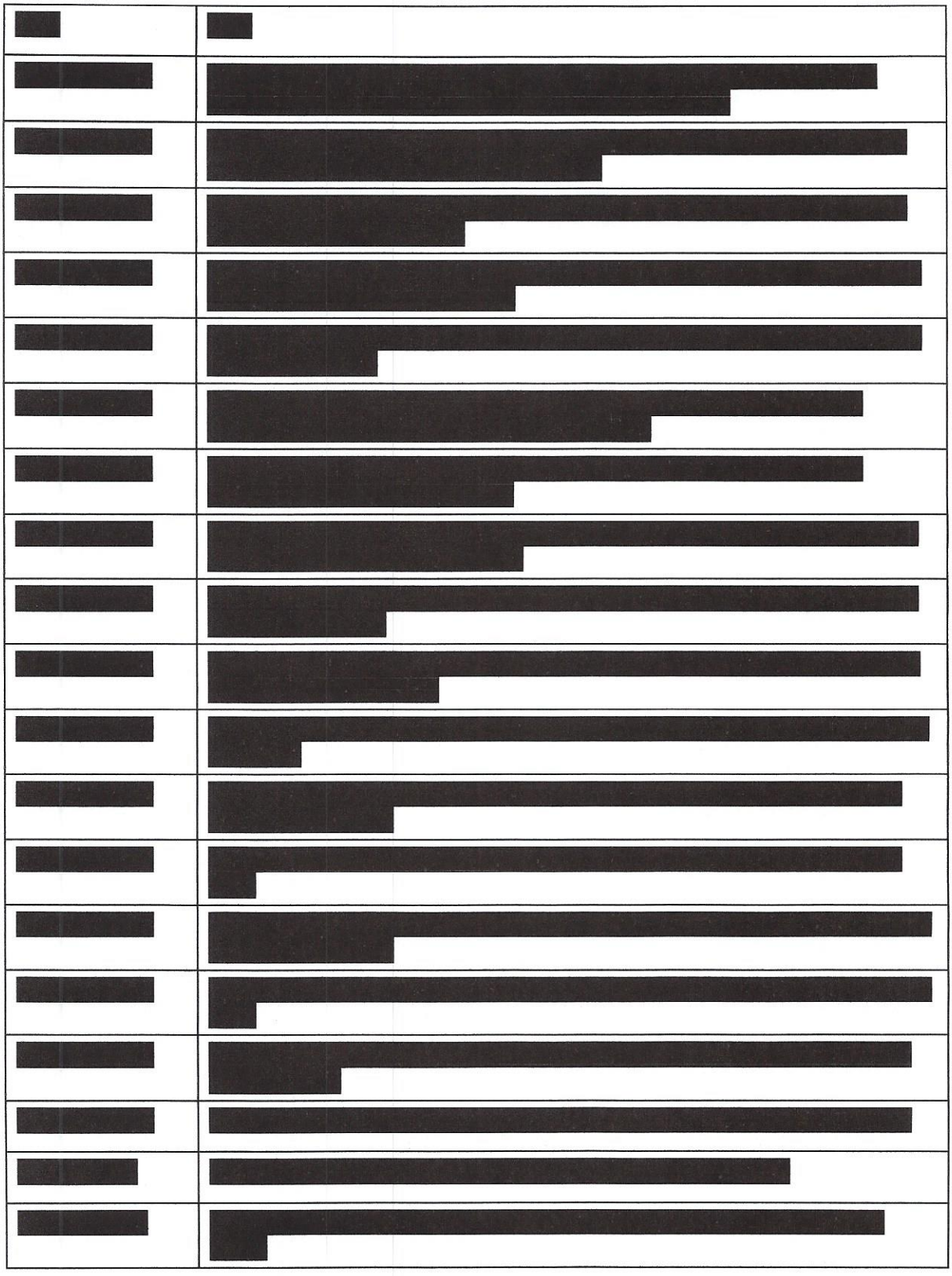

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14. PROGRAMMING SPECIFICATIONS

A separate document will provide the details necessary to replicate the various data imputations outlined in this SAP.