BUT

STATISTICAL ANALYSIS PLAN

Study Title: A Phase 3, Double-blinded, Randomized, Placebo-controlled, Multicenter Study of BUT-03 (Voxelotor) Administered Orally to Patients with Sickle Cell Disease

1 INTRODUCTION

Blood Unit Therapeutics (BUT) is conducting a Phase 3 study (Study BUT-03) evaluating voxelotor for the treatment of sickle cell disease (SCD) in adult and adolescent patients with SCD.

This document describes the statistical methods and analysis outputs to be used in the summary and analysis of data from Protocol BUT-03. This statistical analysis plan (SAP) will be finalized prior to unblinding.

2 STUDY OVERVIEW

This study is a randomized, placebo-controlled, double blind, parallel group, multicenter Phase llI study, evaluating the efficacy of voxelotor at 1500 mg. Subjects meeting enrollment criteria were randomized in a 1:1 ratio to receive a daily dose of voxelotor 1500 mg or placebo. The treatment duration was at minimum 12 weeks and may continue to a maximum of 96 weeks, with a key study endpoint of 72 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, HbS beta-thalassemia, or other sickle cell syndrome variants. A history of at least one VOC in the past 12 months is required for enrollment. Subjects are also required to have Hb levels: $\leq$ 10.5 g/dL and $\geq$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).

3 OBJECTIVES

3.1 Primary Objective:

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

3.2 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 and recticulocyte %.
- To assess the effects of voxelotor as compared to placebo on long term Vaso- Occlusive Crisis (VOC).

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).

Day l

Day 1 is the date of randomization.

Study Day

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

Study Visit

Study Visit is the nominal visits 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.

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 72

Hemoglobin (Hb) response is based on the difference between the value of Hb levels at Week 72

and baseline Hb level. A subject is considered to be a Hb responder if Hb level increase >1g/dL.

Incidences of VOC

Number of events from randomization to end of study.

5 STUDY ENDPOINTS

5.1 Primary Endpoint:

The primary efficacy measure is Hb response at Week 72.

5.2 Secondary Endpoints:

The secondary efficacy endpoints are as follows:

- Change from baseline in hemoglobin at Week 72
- Change and percent change from baseline in hemolysis measures, including unconjugated bilirubin, reticulocytes %.
- Annualized incidence rate of VOC

6 GENERAL STATISTICAL CONSIDERATIONS

6.1 Sample Size and Power

The sample size for the primary analysis of the study, is 182 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 91 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 IWRS. Permuted blocks were used.

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

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 Examination of Subject Subsets

Subgroups defined by subject age group, (adolescent, 12 to <18 years; and adults, 18 to 65 years), baseline HU use (yes, no), baseline VOC history (1, >l) will be analyzed to evaluate the internal consistency of the study outcomes.

6.3.2 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_1: $P_V \neq P_C$

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.

6.3.3 Secondary Efficacy Analyses

1. Change from baseline at Week 72 in Hb: voxelotor 1500 mg vs Placebo
2. Percent change from baseline at Week 72 in unconjugated bilirubin: voxelotor 1500 mg vs. Placebo
3. Percent change from baseline at Week 72 in reticulocyte %: voxelotor 1500 mg vs Placebo

6.3.4 Imputation of Missing Data for Evaluation of Efficacy

If Hb assessment is missing at Week 72, subject will be treated as a non-responder.

- No imputation will be carried out for other types of data and analysis will be performed on completed cases.

7 TIMING OF ANALYSES

When all randomized subjects have reached 72 weeks of study participation or discontinues from study early, and once all data have been cleaned and database frozen for analysis, the efficacy analysis of BUT-03 will be performed according to this SAP.

8 ANALYSIS POPULATIONS

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.

9 STATISTICAL METHODS

Statistical programming and analyses will be performed using established statistical methods. 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 and figures. 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), median, minimum, maximum, inter-quartile range (IQR). Categorical variables will be descriptively summarized by presenting the number (frequency) and percentage in each category.

The statistical analyses will be conducted with the SAS® System or R.

9.1 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.

Demographic data and baseline characteristics, including age, gender, HU use, VOC history, Baseline Hb, Baseline reticulocytes %, Baseline bilurubin will be summarized using descriptive statistics by treatment groups and overall. Age and VOC history will be described as both continuous and categorical variables according to subsets defined section 6.3.1. No statistical testing will be performed.

9.2 Primary Endpoint

9.2.1 Primary Analysis of Hemoglobin Response

The Hb response rate will be analyzed using a Chi-2 test with Yates' correction, or exact Fischer test if Chi-2 is not applicable. Imputation rules outlined in Section 6.3.4 will be applied. Voxelotor group (1500 mg) will be compared to placebo.

9.2.2 Subgroup analyses

Subgroup analyses will be performed for the primary criteria on each subset defined section 6.3.1.

9.3 Secondary Endpoints

Unless otherwise specified, data will be analyzed with respect to Week 72.

9.3.1 Additional Analysis of Hb

Change from baseline in Hb over time up to Week 72 will be analyzed using adjusted ANOVA model (ANCOVA). The fixed effect terms include treatment group, HU use at baseline. Baseline Hb will also be a co-variate. Missing data due to early drop out or missed visit will not be imputed for this analysis. Analysis will be performed on completed cases.

The adjusted mean (lsmean) change from baseline in Hb, estimated from the ANOVA model, with

the estimated standard error and 95% confidence interval (CI), will be presented in a table and graphic format (e.g: forrest plot).

In addition, measures at baseline, at week 72, the absolute and percent changes from Baseline to Week 72 in Hb measure will be presented descriptively via tabulation of descriptive statistics overall and by treatment group.

9.3.2 Change from Baseline to Week 72 in Hemolysis Related Measures

Percent change from baseline over time up to Week 72 in unconjugated bilirubin and reticulocytes %, will be analyzed with a similar ANOVA model and summarized in tabular and graphic format as for change from baseline to Week 72 in Hb (section 9.3.1).

In addition, measures at baseline, at week 72, the absolute and percent changes from Baseline to Week 72 in each hemolysis measure, including absolute reticulocyte, reticulocytes %, and unconjugated bilirubin will be presented descriptively via tabulation of descriptive statistics overall and by treatment group.

9.3.3 VOC up to Week 72

Annualized incidence rate of VOC events at baseline, week 72 and change from baseline will be summarized with descriptives statistics by treatment group and overall.

10 PROTOCOL DEVIATIONS

Protocol deviations as assessed by the study team (and not the statistician) 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.

11 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.