NCT03919799

STATISTICAL ANALYSIS PLAN

A Phase 2, Randomized, Placebo-controlled, Double-blind, Open-label

Extension Multicenter Study to Evaluate the Efficacy and Safety of Belumosudil

(KD025) in Subjects with Diffuse Cutaneous Systemic Sclerosis

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LIST OF ABBREVIATIONS

AE	Adverse event
ADI	Actual dose intensity
ANCOVA	Analysis of covariance
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Class
BID	Twice daily
BMI	Body mass index
CI	Confidence interval
CM	Concomitant medication
CRF	Case report form
CRISS	Combined Response Index in Diffuse Cutaneous Systemic Sclerosis
CTCAE	Common Terminology Criteria for Adverse Events
dcSSc	Diffuse cutaneous systemic sclerosis
DL_{CO}	Diffusing capacity of the lungs for carbon monoxide
ECG	Electrocardiogram
EOT	End of Treatment
FEV_1	Forced expiratory volume (in the first second)
FVC	Forced vital capacity
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
Hb	Hemoglobin
HLGT	High level group term
HRCT	High-resolution computerized tomography
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IND	Investigational New Drug
IRB	Institutional review board
ICH	International Conference on Harmonisation
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treatment
MMRM	Mixed-effects Model of Repeated Measures
Ms	Millisecond

mRSS	Modified Rodnan Skin Thickness Score
PA	Primary analysis
PD	Pharmacodynamic
PDI	Planned dose intensity
PE	Physical exam
PFTs	Pulmonary function tests
PK	Pharmacokinetic
PT	Preferred term
QD	Once daily
QTcF	Corrected QT interval using Fridericia's formula
RDI	Relative dose intensity
RV	Residual volume
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SHAQ-DI	Scleroderma Health Assessment Questionnaire-Disability Index
SOC	System organ class
SSc	Systemic sclerosis
TEAE	Treatment emergent adverse event
TLC	Total lung capacity
VAS	Visual Analog Scale
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes data-handling and statistical procedures to be used for Study KD025--209 as specified in protocol (Amendment No. 4, 27 May 2021): A Phase 2, Randomized, Placebo-controlled, Double-blind, Open-label Extension Multicenter Study to Evaluate the Efficacy and Safety of Belumosudil (KD025) in Subjects with Diffuse Cutaneous Systemic Sclerosis.

Pharmacokinetic (PK), Pharmacodynamic (PD) and exploratory objectives analyses (biomarkers analysis, histology and gene expression analyses) will be described in separate documents.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled “Guidance for Industry: Statistical Principles for Clinical Trials” and the most recent ICH-E3 Guideline, entitled “Guidance for Industry: Structure and Content of Clinical Study Reports.”

2 STUDY SUMMARY

2.1 Study Objectives

2.1.1 Primary objective

- To evaluate the efficacy of belumosudil compared to placebo for the Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) at Week 24 in modified Intent-to-Treatment (mITT) population.

2.1.2 Secondary objectives

- To assess the CRISS for each group at Week 52
- To evaluate the efficacy of belumosudil compared to placebo at Week 24 for:
    - Modified Rodnan skin thickness score (mRSS)
    - Forced vital capacity (FVC)
    - Physician global assessment
    - Patient global assessment
    - Scleroderma Health Assessment Questionnaire-Disability Index (SHAQ-DI)
- To evaluate the efficacy of belumosudil at Week 52 compared to baseline for subjects randomized to belumosudil for the parameters in the bullet above
- To assess changes in lung fibrosis, via high resolution computerized tomography (HRCT), performed at baseline, Weeks 24 and Week 52 only in subjects with ILD at screening.

- To assess the safety of belumosudil compared to placebo in subjects with diffuse cutaneous systemic sclerosis (dcSSc) by examining the percentage of subjects with Treatment-emergent AEs (TEAEs) (Common Terminology Criteria for Adverse Events [CTCAE] v5.0) in subjects with dcSSc

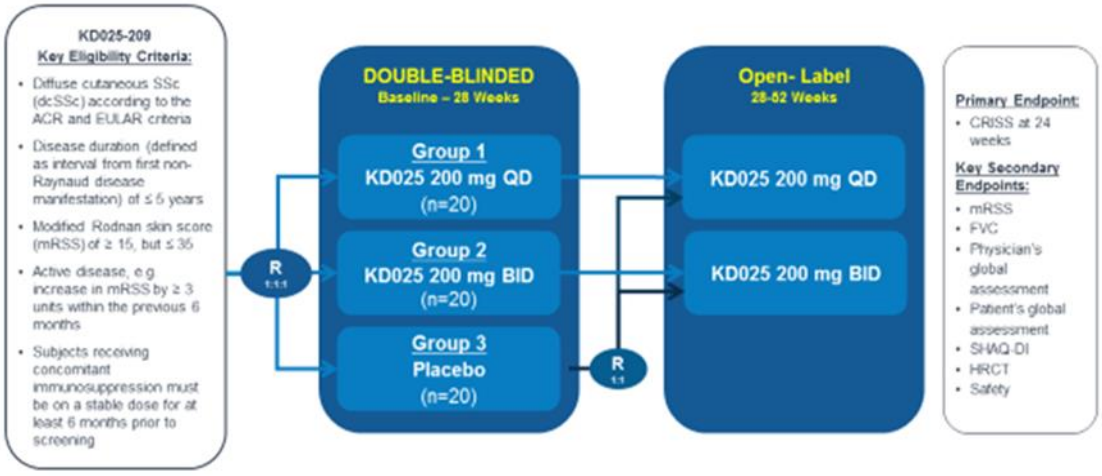
2.2 Study Design

KD025-209 is a Phase 2, placebo-controlled, double-blinded, randomized, multicenter trial in subjects with dcSSc with an open-label extension. The study schematic is shown below in Figure 1.

Subjects who have signed an Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)-approved informed consent form and met all of the inclusion and do not meet all of the exclusion criteria will be enrolled. A total of 60 subjects will be randomized into 3 groups (1:1:1) to receive orally administered belumosudil 200 mg QD (n = 20), belumosudil 200 mg BID (n = 20), or matched placebo (n = 20) for 28 weeks. The study will be double-blinded for the first 28 weeks followed by an open-label extension of 24 weeks. After unblinding, the subjects in Group 1 and 2 will continue on the same belumosudil dose whereas the subjects in the placebo group will be re-randomized to one of the belumosudil doses (200 mg QD or 200 BID) in 1:1 fashion.

Efficacy will be assessed throughout the 52-week dosing period using CRISS, mRSS, PFTs, physician global assessment, SHAQ-DI.

Figure 1 KD025-209 Study Schema



2.3 Visit Schedule and Study Assessment

The flow chart of visit schedule and study assessments is given in Appendix A of the KD025-209 Protocol.

2.4 Treatment Descriptions

The treatment groups will be described below and used for different analysis.

KQD: KD025 200mg QD for the first 28 weeks

KBID: KD025 200mg BID for the first 28 weeks

PBO: Placebo for the first 28 weeks

KQD/KQD: KD025 200mg QD for the first 28 weeks and KD025 200mg QD from week 28 to 52.

KBID/KBID: KD025 200mg BID for the first 28 weeks and KD025 200mg BID from week 28 to 52.

K: KD025 200mg for the first 28 weeks

PBO/KQD: Placebo for the first 28 weeks and KD025 200mg QD from week 28 to 52.

PBO/KBID: Placebo for the first 28 weeks and KD025 200mg BID from week 28 to 52.

KQD_C: KD025 200mg QD for the first 28 weeks combined with subjects that switched from placebo to KD025 200mg QD from week 28 to 52.

KBID_C: KD025 200mg BID for the first 28 weeks combined with subjects that switched from placebo to KD025 200mg BID from week 28 to 52.

K_C: KD025 200mg for the first 28 weeks combined with subjects that switched from placebo to KD025 200mg from week 28 to 52.

All KD025 200mg QD: KD025 200mg QD for the first 52 weeks combined with subjects that switched from placebo to KD025 200mg QD from week 28 to 52.

All KD025 200mg BID: KD025 200mg BID for the first 52 weeks combined with subjects that switched from placebo to KD025 200mg BID from week 28 to 52.

All KD025: KD025 200mg for the first 52 weeks combined with subjects that switched from placebo to KD025 200mg from week 28 to 52.

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Analysis Periods

The analysis will be split into three separate periods.

- The Double-Blinded Period analysis will be the period from week 0 to week 24.
- The Double-Blinded Period (0 – week 28) will be the period from week 0 to week 28.
- The Combined Double-Blinded Period and Open-Label Period will be the period from week 0 to week 52.

3.1.2 Computing Environment

All statistical analyses will be performed using SAS® Version 9.4 or higher for Windows.

3.1.3 Sample Size Justification

This is an exploratory study; sample size and power are not driven by hypothesis testing. A total of 60 subjects will be randomized (1:1:1) to receive orally administered belumosudil 200 mg QD (n = 20), belumosudil 200 mg BID (n = 20), or matched placebo (n = 20).

3.1.4 General Considerations

General considerations for descriptive statistics, presentation, and analysis model (for efficacy analysis) used for continuous and categorical data are given below.

3.1.4.1 Continuous variables

Continuous variables will be described by using these descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum and maximum.

The means, medians, SD, and confidence intervals (CIs) will be reported to one decimal place more than the data reported on the case report form (CRF) or by the laboratory/vendor. Minimum and maximum will be reported to the same number of decimal places displayed on the CRF or by the laboratory/vendor. P-values will be reported to 4 decimal places.

3.1.4.2 Categorical Variables

Frequencies and percentages will be used to describe categorical variables. Some efficacy endpoints with two possible outcomes such as CRISS60 response will be analyzed using logistic model, which is defined in Section 3.1.4.3. When categorical data are presented, the percent will be suppressed when the count is zero in order to draw attention to the nonzero counts. The denominator for all percentages, unless otherwise specified, will be the number of subjects in the treatment group or in the specified analysis population.

3.1.4.3 Logistic Model Used for Efficacy Analysis with Binary Variables

Treatment comparisons of categorical efficacy variables will be assessed using a logistic regression analysis with treatment in the model. The proportions and 95% CI (Clopper-Pearson (exact) method) will be reported. For each treatment comparison, an estimate of the odds ratio, corresponding Wald 95% CI, and p-value will be presented.

3.1.4.4 Mixed-effects Model of Repeated Measures (MMRM) Used for Efficacy Analysis with Continuous Variables

Treatment comparisons of continuous efficacy variables will be assessed using MMRM analysis at all visits including unscheduled visits prior to or at Week 52.

When the MMRM model is used the model includes treatment, visit and treatment*visit interaction as fixed effects, and subject as random effect. For other efficacy variables, the model includes treatment, week, and baseline values as fixed effects, and subject as random effect. For the CRISS Score if the data is not normally distributed then the rank-transformed values will be used instead. The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by compound symmetry will be used. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Type III tests for the LSM will be used for the statistical comparison; the 95% CI will also be reported. Below is the SAS code for the MMRM analysis.

```
Proc mixed DATA=XX;

  Class USUBJID TRT AVISITN ;

  Model AVAL = TRT AVISITN TRT*AVISITN/ ddfm=KENWARDROGER;
```

```
  Repeated AVISITN/Subject=USUBJID type=UN;

  lsmeans TRT*AVISITN/diff=control cl alpha=0.05;

Run;
```

3.1.4.5 Analysis of covariance (ANCOVA) analysis for Efficacy Analysis with Continuous Variables

In addition, treatment comparisons for continuous efficacy variables will also be assessed using an ANCOVA model.

The ANCOVA model includes treatment groups and baseline values. For each treatment comparison performed, the LSM for each treatment group, an estimate of the difference between treatments, corresponding 95% CI and p-value will be presented. Type III sums of squares for the LSM will be used for the statistical comparison. Below is the SAS code for the ANCOVA model.

```
Proc mixed  DATA=XX;

  Class TRT;

  Model AVAL = TRT BASE;

  lsmeans TRT / cl alpha=0.05 pdiff;

Run;
```

3.1.5 Study Day

The study day for all assessments prior to the first study drug administration is calculated as the difference between the date of the event or measurement (e.g., adverse event [AE] onset date, assessment date, sample collection date, etc.) and the start date of study treatment. The day before the start of study treatment is Study Day -1.

The study day for all post assessments after the first study drug administration is calculated as the difference between the date of the event or measurement (e.g., AE onset date, assessment date, sample collection date, etc.) and the start date of study treatment plus one day. The first day of study treatment is Study Day 1.

3.1.6 Baseline

Baseline value is defined as the valid and last non-missing value obtained within 29 days prior to subject receiving the first study medication, unless otherwise stated under the related assessment section. Baseline can be the day before the first study medication or on the same day as the first study medication if a pre-dose assessment is available. Subjects without data on a parameter before the first study medication will have a missing baseline for this parameter.

For patients who randomized in placebo group in double blinded period and re-randomized in open label period, the baseline value of open label period is defined as the valid and last non-missing value obtained prior to subject receiving the first dose of belumosudil.

3.1.7 Handling of Incomplete or Missing Data

The imputed methods for missing data are described as below for the following situations.

3.1.7.1 Imputation for CRISS Score

Linearization and last observation carried forward (LOCF) method will be used when calculating the primary endpoint CRISS if any of the component scores is missing.

The linearization method will be used when there is a missing observation followed by a non missing observation. The missing value will then be imputed as the average of the previous non missing observation and the next non missing observation. If there is no next non missing observation in the current treatment group then just the last observation will be used.

For patients discontinuing investigational product for any reason, the last non-missing observation before discontinuation will be carried forward to the corresponding endpoint for evaluation. For patients randomized to belumosudil at Week 1, the last non-missing observation in double-blind treatment period will be carried forward to open-label treatment period. For patients randomized to placebo at Week 1, LOCF imputation will be performed within treatment period. The last non-missing observation in double-blind treatment period will not be carried forward to open-label treatment period.

Randomized patients without at least 1 postbaseline observation will not be included for evaluation.

3.1.7.2 Missing start and end dates for AE and concomitant medication (CM)

The assumption will be the worst or most conservative judgment when imputing AE and CM start and end dates. The purpose of imputing a start date is to help define whether the AE/CM started while taking study drug.

For a partial or missing start date:

- If the day is missing, the first day of the month will be imputed. If the missing day is the same as the month of first dose of study drug, then the first dose date will be imputed.
- If the day and month are missing, the first day of January will be imputed. If the year is the same as the first dose date, then the first dose date will be imputed.
- If the day is completely missing, the first dose date will be imputed. If the end date suggests it could have started prior to this, the first day of January of the same year as the end date will be imputed.
- When imputing a start date, the start date will ensure that the new imputed date is sensible, i.e., is prior to the end date of the AE or CM.

For a partial or missing end date:

- If the day is missing, the last day of the month or the last assessment date, whichever is earlier, will be imputed.
- If the day and month are missing, the 31st of December or the last assessment date, whichever is earlier, will be imputed.
- If the date is completely missing, there will be a need to look at whether the AE/CM is still ongoing before imputing a date. If the ongoing flag is missing, then it will be assumed that AE is still present, or CM is still being taken (i.e., do not impute a date). If the AE/CM has stopped, then the last assessment date will be imputed.

These data imputations are for categorization purpose only and will not be used in listings.

If the assessment of the relationship of the AE to belumosudil is missing, then it will be assumed that the AE is related to belumosudil and the AE considered as such in the frequency tables of possibly related AEs. No imputation should be done at the data level.

3.2 Analysis Populations

Three populations will be employed in the analysis of study data:

- The Modified Intent-to-treat (mITT) Population will consist of all subjects who receive at least 1 dose of study drug.
- The Evaluable for Efficacy/Activity Population will consist of subjects who have received at least 80% of expected study drug and have post-baseline efficacy data.
- The Safety Population is defined as all subjects who receive at least 1 dose of study drug. In this study, the Safety Population is equivalent to the mITT Population.

The primary endpoint will be analyzed on the modified Intent-to-Treat (mITT) Population.

Demographics, subject disposition, baseline characteristics, and efficacy analyses will be summarized in mITT Population and by group.

All safety analyses will be performed on the safety population.

3.3 Subject Disposition and Evaluability

A disposition of all enrolled subjects will be summarized. The number of subjects screening failed, discontinuing from study treatment, discontinuing from study and the primary reason for discontinuation will be summarized.

3.4 Protocol Deviations

All protocol deviations will be identified and classified as major or minor before the clinical database lock and will be presented in a listing.

Major Deviation: Protocol deviation that may impact the accuracy, and/or reliability of the study data or that may impact subject rights, safety or well-being.

Minor Deviation: Protocol deviation that does not impact the accuracy, and/or reliability of the study data or subject rights, safety or well-being.

3.5 Demographics and Baseline Characteristics

3.5.1 Demographics and Other Characteristics

A summary table and a by patient listing will be generated for patient demographics and other characteristics. Variables to be included are: age, sex, race, ethnicity, height, weight, body mass index (BMI), if subjects with ILD (display ILD confirmed diagnosis date in listing), child bearing potential, and other variables as applicable based on indication/study design.

Demographics and other baseline characteristics will be summarized by treatment group in each population.

3.5.2 Medical History

Medical history (except ILD) will be summarized by primary system organ class (SOC) and preferred term (PT). Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 22.0 or higher) terminology.

Medical history will be presented in a listing by patient and summarized by treatment group in the Safety Population.

3.6 Concomitant Medications

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary. Concomitant medications are all medications taken after the start of study consent, during the treatment period (day 1 until 28 days after last dose), including those started before but ongoing at the start of study treatment.

Concomitant medications will be summarized according to Anatomical Therapeutic Class (ATC) and preferred drug name.

Concomitant medications will be presented in a listing by patient and summarized by treatment group in the Safety Population.

3.7 Treatment Compliance and Exposure

The relative dose intensity (RDI) will be used to assess the treatment compliance. The RDI is defined as:

$$\text{RDI (\%)} = 100 \times \text{ADI (mg/day)} / \text{PDI (mg/day)},$$

where ADI and PDI are the actual dose intensity and planned dose intensity, respectively:

PDI (mg/day) = planned cumulative dose (mg) / duration of exposure (days),

ADI (mg/day) = actual cumulative dose (mg) / duration of exposure (days).

The planned cumulative dose is the planned daily dose amount multiplied by the duration of exposure, while the actual cumulative dose is the sum of actual total daily dose amount over the duration of exposure. The actual total daily dose will need the information of dose modifications (increased and reduced) and dose interruption (held) captured in CRF (Dose Modifications and Interruptions). If a subject does not take any study drug, the actual RDI by definition is zero.

The duration of exposure is defined as:

Duration of exposure (days) = (Date of last dose – Date of first dose) + 1, regardless of unplanned intermittent discontinuations.

One summary table will be generated for treatment exposure and compliance, including: treatment duration (weeks), treatment duration categories (0 to 12 weeks, 12 to 24 weeks, 24 to 28 weeks, 28 to 40 weeks, 40 to 52 weeks), actual cumulative dose, ADI, RDI, and RDI categories (>80%, <=80%; >95%, <=95%).

Another summary table will be generated for dose increased, dose reduced, dose held, and the reasons.

A by patient listing will be generated for the detailed exposure information.

It will be summarized in Safety Population and by group.

3.8 Definition of Efficacy Endpoints

3.8.1 Primary Efficacy Endpoint: CRISS

The primary efficacy endpoint is Combined Response Index in Diffuse Cutaneous Systemic Sclerosis (CRISS).

CRISS is a 2-step process for use in a clinical trial.

Step 1: patients who develop new onset of renal crisis, new onset or worsening of lung fibrosis, new onset of pulmonary arterial hypertension, new onset of left ventricular failure during the trial are considered as not improved and assigned a probability of improving equal to 0.0.

Step 2: For the remaining patients, step 2 involves computing the predicted probability of

improving for each individual, using the equation shown below.

$$\frac{\exp\left[-5.54 - 0.81 * \Delta_{MRSS} + 0.21 * \Delta_{FVC\%} - 0.40 * \Delta_{Pt-glob} - 0.44 * \Delta_{MD-glob} - 3.41 * \Delta_{HAQ-DI}\right]}{1 + \exp\left[-5.54 - 0.81 * \Delta_{MRSS} + 0.21 * \Delta_{FVC\%} - 0.40 * \Delta_{Pt-glob} - 0.44 * \Delta_{MD-glob} - 3.41 * \Delta_{HAQ-DI}\right]}$$

where Δ_{MRSS} indicates the change in mRSS from baseline to follow up, $\Delta_{FVC\%}$ denotes the change in FVC% predicted from baseline to follow up, $\Delta_{Pt\text{-}glob}$ indicates the change in patient global assessment, $\Delta_{MD\text{-}glob}$ denotes the change in physician global assessment, and $\Delta_{HAQ\text{-}DI}$ is the change in HAQ-DI. All changes are absolute change ($Time_2$-$Time_{baseline}$).

As patient global assessment and physician global assessment are based on a VAS of 0 (Extremely Poor)-100 (Excellent) in CRF. When calculating the CRISS score, these 2 scores should be divided by 10 firstly to make it in a 0-10 scale. If any of the component scores are missing, CRISS score will be calculated based on the imputed component score using LOCF method.

The outcome is a continuous variable between 0.0 and 1.0 (0-100%). A higher score indicates greater probability of improvement. A CRISS score ≥ 20% is considered as the minimal detectable difference and will be described as CRISS20 in the SAP. A CRISS score >= 60% is considered as the minimally important difference and will be described as CRISS60 in the SAP. This will be the primary variable for efficacy.

Analyses of the primary efficacy endpoints will be conducted using the mITT population. The number and percentage of patients achieving CRISS60 response will be summarized by treatment group. Treatment comparisons between each belumosudil dose regimen and placebo in the proportion of patients achieving an CRISS60 response will be analyzed using a logistic regression analysis with treatment in the model.

The continuous CRISS score will be summarized as a continuous endpoint at all post baseline scheduled assessment visits. The continuous CRISS score will be analyzed using the MMRM model, and a t-test comparison. If the data is not normally distributed then the Wilcoxon-Mann-Whitney model will be used instead of a t-test. Missing data will be imputed using the Linearization method The linearization method will take the average of the last observation and the next non missing observation. If there is no next non missing observation in the current treatment group then just the last observation will be used.

3.8.2 Secondary Efficacy Endpoints

3.8.2.1 mRSS

The mRSS is a measure of skin thickness rated with scores ranging from zero (0; normal) to three (3; severe skin thickening) across 17 different sites. The total score is the sum of the individual skin scores in the 17 body areas (e.g., face, hands, fingers; proximal area of the arms, distal area of the arms, thorax, abdomen; proximal area of the legs, and distal area of the legs, feet), giving a range of 0-51 units. A negative change from baseline demonstrates improvement.

MRSS total score, change from baseline, percent improvement will be summarized as a continuous endpoint at all scheduled assessment visits.

The change from baseline and percent improvement in mRSS total score will be analyzed using the MMRM model. In addition, the change from baseline and percent improvement in mRSS total score will be analyzed using the ANCOVA model. Missing data will not be imputed.

3.8.2.2 PFTs

Onset/progression of ILD will be evaluated by the effect of belumosudil compared to placebo in the change in predicted FVC, which is based on institutional standards and will be measured as part of PFTs, including FEV1, FVC, DL_{CO}, TLC, and RV.

FVC (%) and change from baseline will be summarized as a continuous endpoint at all scheduled assessment visits. The change from baseline in FVC (%) will be analyzed using the MMRM model. In addition, the change from baseline will be analyzed using the ANCOVA model. Missing data will not be imputed.

FEV1, FVC, DL_{CO}, TLC, RV and their change from baseline will be summarized as a continuous endpoint in subjects with ILD at screening.

3.8.2.3 Physician Global Assessment

Physician global assessment is physician’s assessment of patient's overall health during the last week based on a VAS of 0 (Extremely Poor)-100 (Excellent). A positive change from baseline demonstrates improvement.

Physician global assessment score, change from baseline, percent improvement will be summarized as a continuous endpoint at all scheduled assessment visits.

The change from baseline and percent improvement in physician global assessment score will be analyzed using the MMRM model. In addition, the change from baseline and percent improvement in physician global assessment score will be analyzed using the ANCOVA model. Missing data will not be imputed.

3.8.2.4 Patient Global Assessment

Patient global assessment is patient's assessment of their overall health during the last week based on a VAS of 0 (Extremely Poor)-100 (Excellent). A positive change from baseline demonstrates improvement.

Patient global assessment score, change from baseline, percent improvement will be summarized as a continuous endpoint at all scheduled assessment visits.

The change from baseline and percent improvement in patient global assessment score will be analyzed using the MMRM model. In addition, the change from baseline and percent improvement in patient global assessment score will be analyzed using the ANCOVA model. Missing data will not be imputed.

3.8.2.5 SHAQ-DI

SHAQ-DI includes the general HAD-DI assessment and 6 scleroderma-specific Visual Analog Scale (VAS) items to explore the impact of participant's disease. The general HAD-DI assessment includes 8 sections: dressing, arising, eating, walking, hygiene, reach, grip, and activities. The 6 VAS items will be rated separately in scale of a 0−100 millimeters [mm], with higher scores indicating more severe disease. The 6 items are: 1) pain, 2) intestinal disease, 3) breathing problem, 4) Raynaud syndrome, 5) finger ulcers, and 6) overall disease. A negative change from baseline demonstrates improvement.

SHAQ-DI total score, each of the 6 VAS scores and their change from baseline, percent improvement will be summarized as a continuous endpoint at all scheduled assessment visits.

The change from baseline and percent improvement in each SHAQ-DI score will be analyzed using the MMRM model. In addition, the change from baseline and percent improvement in patient global assessment score will be analyzed using the ANCOVA model. Missing data will not be imputed.

3.8.2.6 HRCT

Changes in lung fibrosis for patients with ILD at screening will be assessed using HRCT. Pure Ground-Class Opacity, Pulmonary Fibrosis and Honeycombing were recorded for each lung and three lung zones. They are recorded categorically for the amount detected, ranging from Absent to >75%. These will be summarized and change from baseline will be compared between treatment groups.

3.8.2.7 Treatment Emergent Adverse Events

Treatment emergent adverse events at Week 24 will be compared between treatment groups and placebo for subjects with dcSSc at baseline.

3.9 Safety Analysis

Safety assessments include AEs, serious adverse events (SAEs), vital sign measurements, clinical laboratory evaluations (hematology, chemistry) and electrocardiograms (ECGs). Unscheduled visits for safety assessments will not be presented in by visit summary tables but will be in listings and shift tables. All safety analyses will be performed using the safety population.

Clinically significant PE findings will be captured as AEs.

3.9.1 Adverse Events

AEs will be coded using the MedDRA dictionary (Version 22.0 or higher). TEAEs are any AEs occurring or worsening in severity after the first administration of study medication. All AEs (including SAEs) will be graded using the 5-point CTCAE V5.0 scale (mild, moderate, severe, life threatening, or death). Causality with study treatment will be classified as: definitely related; probably related; possibly related; unlikely related; not related.

The number (N) and percentage (%) of patients who experienced at least one TEAE will be summarized by dose group, including tabulation by:

- SOC and PTs within each SOC in decreasing total frequency
- PT in decreasing total frequency
- SOC, PTs, and maximum severity
- SOC, PTs, and relationship to study drug

These analyses will be repeated for Grade ≥3 TEAEs, SAE, TEAEs leading to dose modification, and AE leading to study drug discontinuation.

Subject listings will be provided for AEs, SAEs, AEs resulting in study drug discontinuation and deaths. Time to onset and duration of AEs will be included in listings, along with action taken and outcome.

3.9.2 Clinical Laboratory Evaluation

The summary statistics (including number, mean, SD, median, minimum and maximum) of all laboratory variables and changes from baseline will be calculated for each visit or study assessment by treatment group.

For parameters of white blood cell counts, neutrophils (absolute count), lymphocytes (absolute count), monocytes (absolute count), Hb, platelets, ALP, ALT, AST, GGT, total bilirubin, GFR, plots of mean / mean changes from baseline with the corresponding standard error will be displayed.

For shift tables, laboratory results will be classified using the CTCAE V5.0. All graded laboratory parameters will be summarized separately for hematology and biochemistry. Corresponding shift tables to compare baseline to the worst post-baseline grade within the treatment period will be provided.

A by patient by lab tests by visit listing will be generated for lab results with CTC grade >=3.

3.9.3 Vital Signs

Descriptive statistics for vital signs (weight, heart rate, body temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate) values and the change from baseline will be presented by treatment group for each scheduled assessment time point.

A by patient by visit listing will be generated for vital signs.

3.9.4 ECG

Descriptive statistics for ECG parameters (i.e., heart rate, PR interval, RR interval, QRS interval, QT interval, and QTcF interval) at each time point with triplicate ECGs will be presented for the values and change from baseline scores (QTcF is the QT interval using Fridericia's correction which is calculated by $QTcF = QT/RR^{1/3}$). In addition the maximum change from baseline will be calculated for each subject and summarized for each treatment group.

The number and percentage of subjects with observed QTcF values that satisfy the following conditions will be presented by treatment group and study visit:

- ≤ 450 millisecond (ms)
- >450 to ≤ 480 ms
- >480 to ≤ 500 ms
- > 500 ms

The number and percentage of subjects having change from baseline QTcF values that satisfy the following conditions will be presented by treatment group and study visit:

- ≤ 0 ms
- >0 to ≤ 30 ms
- >30 to ≤ 60 ms
- > 60 ms

A by patient by visit listing will be generated for ECG results.

3.10 Pharmacokinetic Analysis

Further details will be described in the Pharmacokinetic Analysis Plan.

3.11 Pharmacodynamics Analysis

Further details will be described in the Pharmacodynamics Analysis Plan.

3.12 Exploratory Objectives Analysis

The exploratory objectives are listed as below and will be described in the Exploratory Analysis Plan.

- To evaluate changes in biomarkers of endothelial cell dysfunction, fibrosis, immune system function, and cytokine alterations from subjects receiving belumosudil or placebo

- To assess histology and gene expression from skin biopsies taken from subjects at baseline, Week 24 and optionally at Week 52

4 REFERENCES

1. Khanna D, Berrocal VJ, Giannini EH, Seibold JR, Merkel PA, Mayes MD, et al. The American College of Rheumatology provisional composite response index for clinical trials in early diffuse cutaneous systemic sclerosis. Arthritis Rheumatol. 2016;68(2):299–311.

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