STATISTICAL ANALYSIS PLAN

A Randomized, Phase 2, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Activity of KD025 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

Protocol Number: KD025-207

Statistical Analysis Plan Version:	Date of Statistical Analysis Plan:
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DOCUMENT HISTORY

Version	Author	Description
1.0	Zhongming Yang	New Document

2.0	Zhongming Yang	Revision
		The primary reasons for this new version include:
		• Add St. George's Respiratory Questionnaire as secondary efficacy endpoint
		• Add options to accommodate the following issues for mixed/ANCOVA models:
		  o Nonconvergence
		  o Validity of linear model assumptions
		• Format and clean list of TLFs
		• Other minor formatting or organization changes

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
6MWD	6- minute walking distance
AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
BSC	standard of care
CCL-18	chemokine ligand 18
CRF	case report form
CSR	clinical study report
DL_{CO}	diffusing capacity of carbon monoxide
FVC	forced vital capacity
HLGT	high level group term
HRCT	high-resolution computed tomography
ICH	International Conference on Harmonisation
IPF	idiopathic pulmonary fibrosis
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
mL	Milliliter
MMP7	matrix metalloproteinase-7
Msec	Millisecond
PE	physical exam
PFTs	pulmonary function tests
PT	prothrombin time
PT	preferred term
PTT	partial thromboplastin time
QD	once-daily
QTcF	corrected QT interval using Fridericia's formula
RV	residual volume
SAE	serious adverse event
SAP	statistical analysis plan
SGRQ	St. George's respiratory questionnaire
SOC	system organ class
SPD	surfactant protein-D
SpO_2	pulse oximeter oxygen saturation
TEAE	treatment emergent adverse event
WHO	World Health Organization

1 INTRODUCTION

This study, KD025-207, is being conducted to evaluate the safety, tolerability, and activity of 400 mg of KD025 once-daily (QD) compared to best supportive care (BSC) in subjects with Idiopathic Pulmonary Fibrosis (IPF) previously treated with or offered pirfenidone and/or nintedanib.

This Statistical Analysis Plan (SAP) describes data-handling and statistical procedures to be used for the analysis and reporting of efficacy and safety data collected under Study KD025-207 (Amendment 8 20-Sep-2019) and presented in the clinical study report (CSR). This SAP has been developed and finalized prior to locking the clinical database.

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

Primary objectives:

- To evaluate the change in forced vital capacity (FVC) from baseline to 24 weeks after dosing with KD025 400 mg QD in subjects with IPF compared with BSC.

- To evaluate the safety and tolerability of KD025 400 mg QD when administered for 24 weeks to subjects with IPF compared to BSC.

Secondary objectives:

- To evaluate the change in 6-minute walk distance (6MWD) from baseline to 24 weeks

- To evaluate the occurrence of acute exacerbation of IPF (frequency and severity) throughout treatment

- To evaluate change in severity of lung fibrosis as measured by quantitative high-resolution computed tomography (HRCT)

- To evaluate the percentage of subjects with disease progression before or at 24 weeks

- To evaluate the change in score of St. George's Respiratory Questionnaire (SGRQ) from baseline to 24 weeks

Exploratory Objective

- To evaluate the change in matrix metalloproteinase-7 (MMP7), chemokine ligand 18 (CCL-18), and surfactant protein-D (SPD) serum levels

2.2 STUDY DESIGN

This is a Phase 2, randomized (2:1), open-label, multicenter study in subjects with IPF. Eighty-one (81) subjects with IPF who are eligible will be randomly enrolled in a 2:1 ratio (KD025 to BSC) to one of two treatment groups. Subjects randomized to Treatment Group 1 will receive KD025 400 mg QD orally for 24 weeks. Subjects randomized to Treatment Group 2 will receive BSC (as deemed appropriate by the investigator).

Subjects may continue to receive therapy with KD025 beyond week 24, for total treatment duration of up to 96 weeks. Subjects receiving BSC (Treatment Group 2) have the option of switching to therapy with KD025 at any time during the first 6 months of the study (up to and including Amendment 5). Starting from Amendment 6, subjects receiving BSC have the option to switch to therapy with KD025 after week 24.

2.2.1 Number of Subjects

Approximately eighty one subjects with IPF.

2.2.2 Efficacy Assessments

2.2.2.1 Pulmonary function testing

Pulmonary function testing will be performed at screening, baseline, then every 12 weeks on study (12 weeks, 24 weeks, 36 weeks etc.) and at a 30-day Follow-up visit. Pulmonary function testing will include FVC, residual volume (RV), and diffusing capacity of carbon monoxide (DL_{CO}).

2.2.2.2 Six minute walking distance (6MWD)

Six minute walking distance (6MWD) will be assessed at the same times as pulmonary function tests (PFTs), in accordance with published guidelines. The total distance ambulated in meters during the 6-minute walk is recorded. The 6MWD, heart rate, blood pressure, pulse oximeter oxygen saturation (SpO_2) are recorded before and after the walk.

2.2.2.3 Occurrence of acute exacerbation of IPF

Occurrence of acute exacerbation of IPF (frequency and severity) will be assessed throughout the study. The following clinical deterioration symptoms within a month that cannot be explained by other reasons will be assessed as acute exacerbation:

1. Aggravated dyspnea;
2. Newly discovered chest interstitial lung abnormality by radiograph/HRCT, without pneumothorax or pleural effusion;
3. SpO_2 decreases to < 88% (heart failure or pulmonary embolism excluded).

Acute exacerbation can be diagnosed if Items 1 and 2 are present or if Items 1 and 3 are present and the following AEs have not occurred:

- Any AE with the Preferred term containing the word "infection"
- Pulmonary embolism (Preferred Term)
- Pneumothorax (Preferred Term)
- Any AE with the Preferred Term containing the word "Cardiac failure"

If any of these AEs occurred with a start date in the period between the date of the IPF assessment and the previous scheduled visit (+ 1 day so as to not include the day of the previous visit), the event will not be considered an acute exacerbation of IPF.

2.2.2.4 The change in severity of lung fibrosis

The change in severity of lung fibrosis will be determined using measurements from quantitative HRCT.

2.2.2.5 Time to progression of IPF

Time to progression of IPF is defined as time from the Week 1 Day 1 visit to the first occurrence of any of the following:

1. First respiratory-related hospitalization.
2. Respiratory-related death.
3. Absolute decline in FVC percent of predicted value of ≥ 10% versus FVC percent of predicted value recorded at baseline.
4. Absolute decline in DL_{CO}, adjusted for hemoglobin, percent of predicted value of ≥15% versus DL_{CO} recorded at baseline.

Note: the following conventions will be used for assessing these criteria:

First respiratory-related hospitalization

- Any AE where the High Level Group Term (HLGT) contains the terms "respiratory" (case insensitive) and the AE resulted in a hospitalization (as determined by the AE Serious Check box "Result in initial or prolonged hospitalization").

Respiratory-related death

- Any AE where the High Level Group Term (HLGT) contains the terms "respiratory" (case insensitive) and the AE resulted in a "death".

2.2.2.6 St. George's respiratory questionnaire (SGRQ) [1]

SGRQ is a disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. There are following two parts: a) symptoms component (frequency & severity) with a 3-month recall; b) activities that cause or are limited by breathlessness; Impact components (social functioning, psychological disturbances resulting from airways disease) refer to current state as the recall. SGRQ score will be calculated by an Excel-based scoring Calculator licensed from St George's University of London.

SGRQ scores range from 0 to 100, with higher scores indicating more limitations. Based on empirical data and interviews with patients, a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment[2,3].

2.2.3 Safety Assessments

The primary safety outcome will be the percent of subjects in each treatment group experiencing AEs.

Safety assessments include AEs, serious AEs (SAEs), physical exams (PEs), vital sign measurements, clinical laboratory evaluations, and ECGs. Reasons for treatment discontinuation because of toxicity will be documented. Safety assessments will be performed at specified time points and before discharge from the clinic.

The AE reporting period for a subject enrolled in the study begins when the subject signs the informed consent and is continued through 28 days after their last dose of KD025. For BSC subjects, AEs will be reported through the End-of-Week 24 visit.

Vital sign measurements, including blood pressure, pulse rate, respiratory rate, and temperature will be monitored throughout the study.

2.2.4 Pharmacodynamic Assessments

Serum levels for MMP7, CCL18, and SPD will be assessed at baseline and every 12 weeks in study.

2.2.5 Study Assessment Summary

Detailed study assessments and schedule are listed in Table 1 "Study Assessments" in study protocol.

3 STATISTICAL METHODS

3.1 General Methods

3.1.1 Computing Environment

All statistical analyses will be performed using SAS® Version 9.3 or higher for Windows.

3.1.2 Reporting of Numerical Values

All clinical study data will be presented in patient data listings

Continuous data will be described using descriptive statistics: number of observations (n), mean, standard deviation, median, minimum and maximum. Frequencies and percentages will be used for summarizing categorical data. 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 specified analysis population or group.

Means, medians, standard deviations, and confidence intervals 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.

3.1.3 Efficacy Analysis Methods

3.1.3.1 Subgroup analyses

The following subgroup analyses will be conducted for major efficacy and safety endpoints:

- Prior treatment of either Nintedanib or Pirfenidone
- Baseline GAP stage

The GAP model[4] consists of four baseline variables: gender (G), age (A) and two lung physiology variables (P) (FVC and DL_{CO}). GAP index is the summation of individual points from Table 1. Three stages, I, II and III, were identified based on the GAP index as defined in the same table.

Table 1 Definition of GAP stage

	Predictor		Points
	Gender		
G		Female	0
		Male	1
	Age years		
A		≤60	0
		61-65	1
		>65	2
	Physiology		
	FVC % predicted		
		>75	0
		50-75	1
		≤50	2
P	DL_{CO} % predicted		
		>55	0
		36-55	1
		≤35	2
		Cannot perform	3
Maximum possible index = 8. Stage is defined according to index as I (0-3), II (4-5), III (6-8).			

3.1.3.2 Mixed model

The following mixed model will be used to estimate and compare rate of change from baseline for FVC percent of predicted value, FVC (mL), 6MWD and other applicable endpoints

$$y_i(t) = intercept + \alpha \cdot y_i(0) + \Delta y_{BSC} \cdot BSC \cdot t + \Delta y_{KD} \cdot KD \cdot t + \Delta y_{sf} \cdot sf \cdot t + a_i + b_i \cdot t + \varepsilon_i(t)$$

where,

- t is weeks since baseline or cross over
- Δy_x is the change rate of efficacy endpoint y caused by factor x
- BSC and KD is treatment indicator
- i is the patient id
- sf is the categorical variable for subgroup factor
- a and b are random effects dual to individual patient
- $\varepsilon_i(t)$ is the random error

Treatment effect will be calculated by point estimate, 95% confidence interval and p value of $\Delta y_{KD},\ \Delta y_{BSC}\ and\ \ \Delta y_{KD} - \Delta y_{BSC}$.

If there is a convergent issue due to small sample size, following approaches should be tried sequentially:

- Use ANCOVA model

$$y_i(t) = intercept + \alpha \cdot y_i(0) + \Delta y_{BSC} \cdot BSC \cdot t + \Delta y_{KD} \cdot KD \cdot t + \Delta y_{sf} \cdot sf \cdot t$$

- Use ANCOVA model

$$y_i(t) = intercept + \alpha \cdot y_i(0) + \Delta y_{BSC} \cdot BSC \cdot t + \Delta y_{KD} \cdot KD \cdot t$$

If the linear model assumptions are not satisfied through residual analyses, only descriptive statistics will be provided.

3.1.3.3 Proportion Difference

Proportion difference and its confidence interval will be calculated with Wilson (score) method.

3.1.4 Hypothesis Testing and Multiplicity Adjustment

This study is designed as an exploratory, proof-of-concept study, and p values serve as tools for exploration rather than strict criteria for accepting or rejecting various hypotheses. There will be no multiplicity adjustment.

3.1.5 Baseline Value and Change from Baseline (if applicable)

Baseline value is defined as the average of screening and week 1 most recent non-missing value obtained immediately prior to randomization (i.e., generally the study day 1 assessment which occurs pre-randomization) if their visit dates are 28 or fewer days apart, otherwise is defined as the week 1 most recent non-missing value. The crossover baseline value is defined as the average of the last BSC value and cross over W1D1 value if their visit dates are 28 or fewer days apart, otherwise is defined as the cross over W1D1 value.

3.1.6 Handling of Missing/Incomplete Values

Unless otherwise explicitly specified, missing data will not be imputed; observed cases will be used in the analyses.

3.2 Analysis Populations

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

- The safety population will consist of all subjects who are randomized and receive at least 1 dose of KD025 (Treatment Group 1) or have week 1 assessment for BSC subjects. All safety analyses will be performed on the safety population.

- The modified intent-to-treat (mITT) population will consist of all subjects in the safety population who have evaluable baseline and at least one evaluable post baseline FVC assessment. Only evaluable FVC will be used in efficacy.

- The per-protocol (PP) population will consist of all subjects in the safety population who have evaluable baseline and evaluable week 24 FVC assessment. For any analysis on per-protocol population, patient should assigned to treatment actually received, and re-calculated baseline value should be used for cross over patients.

There will be following four treatment groups in all descriptive efficacy and safety tables except otherwise specified.

1. KD025 as randomized
2. BSC as randomized
3. ALL KD025 treated: KD025 as randomized and KD025 data for crossed over subjects after cross over
4. BSC without cross over: data for those randomized to BSC up to the point of cross over

3.3 Patients Disposition and Evaluability

A disposition of all enrolled subjects will be provided. This will include the number and percentage of patients evaluated for each of the analysis populations (Section 3.2) by treatment group and overall. The number of patients discontinuing from the study and the primary reason for discontinuation will also be summarized.

3.3.1 Protocol Deviations

A listing of protocol deviations will be presented by treatment group.

3.4 Demographics and Baseline Characteristics

3.4.1 Demographics

Patient demographics and baseline characteristics will be summarized for the safety Populations.

Descriptive statistics will be provided for age, height, weight, and body mass index Frequencies and percentages will be tabulated for sex, race, and ethnicity.

Age will be calculated as (informed consent date – date of birth + 1)/365.25, truncated and displayed as years. BMI will be calculated as weight (kg)/height^2 (m^2), using the weight and height measurements obtained at baseline (or screening if missing at baseline).

3.4.2 Medical History

Medical history will be collected and summarized by treatment group and overall for mITT population.

3.4.3 IPF History

The following IPF history will be summarized by treatment group and overall for safety population:

- Smoking history
- Time since diagnosis
- Prior pirfenidone
- Prior nintedanib
- FVC decline in 1 year prior to randomization (by mixed model and descriptive statistics)
- Presence of aggravated dyspnea within the previous 6 months prior to signing of informed consent? (yes/no)

3.5 Prior and Concomitant Medications/Procedures

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary and the data will be summarized by treatment group and presented in tables and listings. Incidence of prior and concomitant medication will be presented by preferred (generic) drug name for each treatment group and overall.

Prior medications are those that started and stopped before randomization; concomitant medications are all medications taken after randomization, during the study period, including those started before but ongoing at randomization. Where a

medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

3.6 Treatment Compliance and Exposure

3.6.1 Exposure to KD025

The number of days on study will be calculated as last visit date – first visit date + 1. The exposure to KD025will be calculated by the number of days on study treatment (last dose date – first dose date + 1). Descriptive statistics of days on study and overall exposure will be tabulated and presented by subject in data listings.

3.6.2 Compliance to Study Treatment

Compliance with study drug will presented for the KD025 treatment group and cross over patients.

Compliance rates will be derived with the following formula:

100* ((Total days in study – days missed dose)/ (Total days in study)).

Descriptive statistics of compliance rates will be tabulated and presented by subject in data listings.

3.6.3 Dose Modifications

The incidence of dose modifications for the KD025 treatment group will be summarized, including the percentage of dose reductions, drug holds, and reasons for dose modifications.

3.7 Efficacy Analysis

3.7.1 Primary Efficacy Endpoints and Analyses

3.7.1.1 W24 FVC (Volume, mL)

- The change from baseline to W24, using data up to and including W24 and using the mixed model described in section 3.1.3.2, will be reported for each group defined in section 3.2
- The difference in the change from baseline at W24 will be analyzed for the following:
    - Groups 3 (All KD025 treated) and Group 4 (BSC without crossover)
    - Groups 1 (KD025 as randomized) and Group 4

3.7.1.2 W24 FVC (% predicted)

The analyses described in section 3.7.1.1 for FVC (Volume, mL) will be repeated for FVC (% predicted)

3.7.2 Secondary Efficacy Endpoints and Analyses

3.7.2.1 FVC (Volume, mL)

- The change from baseline to W48 and W96, using data up to and including W48 and W96 respectively and using the mixed model described in section 3.1.3.2, will be reported for groups 1 and 3.

3.7.2.2 FVC (% predicted)

- The analyses described in section 3.7.2.1 for FVC (Volume, mL) will be repeated for FVC (% predicted)
- The proportion of subjects with ≥5% and ≥10% declines in FVC %predicted from baseline to week 24 will be reported for each group defined in section 3.2.
    - The differences in the proportions will be analyzed for the following:
        i. Group 3 and Group 4
        ii. Group 1 and Group 4
- The proportion of subjects with ≥5% and ≥10% declines in FVC %predicted from baseline to W48 and W96 will be reported for groups 1 and 3

3.7.2.3 6MWD

- The change from baseline to W24, using data up to and including W24 and using the mixed model described in section 3.1.3.2, will be reported for each group defined in section 3.2
    - The difference in the change from baseline at W24 will be analyzed for the following:
        i. Group 3 and Group 4
        ii. Group 1 and Group 4
- The proportion of subjects with ≥50m declines in 6MWD from baseline to week 24 will be reported for each group defined in section 3.2.
    - The differences in the proportions will be analyzed for the following:
        i. Group 3 and Group 4
        ii. Group 1 and Group 4
- The change from baseline to W48 and W96, using data up to and including W48 and W96 respectively and using the mixed model described in section 3.1.3.2, will be reported for groups 1 and 3.
- The proportion of subjects with ≥50m declines in 6MWD from baseline to W48 and W96 will be reported for groups 1 and 3.

3.7.2.4 DLco (Corrected for Hemoglobin)

The analyses described in section 3.7.2.3 for 6MWD will be repeated for hemoglobin corrected DLco
DLCO Predicted Corrected = DLCO Predicted * (1.7 * Hgb /(Age-Sex-Factor + Hgb))
where, Age-Sex-Factor is

- 9.38 for females of any age, and children less than 15 years old
- 10.22 for males 15 years old or older

The cutoff criterion for proportion calculation uses 15% decline instead of 50m decline.

3.7.2.5 Lung Fibrosis as Measured by Quantitative HRCT

- The change from baseline to W24, using data up to and including W24 and using the mixed model described in section 3.1.3.2, will be reported for each group defined in section 3.2
    - The difference in the change from baseline at W24 will be analyzed for the following:
        i. Group 3 and Group 4
        ii. Group 1 and Group 4
- The change from baseline to W48 and W96, using data up to and including W48 and W96 respectively and using the mixed model described in section 3.1.3.2, will be reported for groups 1 and 3.

3.7.2.6 Descriptive statistics for FVC, 6MWD, DLco

Descriptive statistics (n, mean, std, median, min, max) of FVC, 6MWD and DLco, and their change from baseline will be tabulated by treatment group and study visits

For proportions, descriptive statistics (n, %) will also be tabulated by treatment groups and total.

3.7.2.7 Descriptive statistics for lung fibrosis throughout the treatment period

Descriptive statistics (n, mean, std, median, min, max) in severity of lung fibrosis as measured by quantitative HRCT (total fibrosis, reticular abnormality, honeycombing scores) on baseline, week 24, 48 and 96 and change from baseline will be summarized by treatment group.

3.7.2.8 Acute exacerbation of IPF throughout the treatment period

The incidence of patients who had an acute exacerbation of IPF throughout the treatment period by study visit will be presented by treatment group and will be compared by means of a Fisher's exact test on week 24.

Kaplan Meier curves and descriptive statistics will also be used to summarize time to IPF exacerbation.

3.7.2.9 Time to IPF progression

Kaplan-Meier curves and descriptive statistics will be used to summarize time to disease progression. Log-rank test will be used for comparing treatment difference. BSC patients will be censored on cross over.

3.7.2.10 Time to first respiratory-related hospitalization

Kaplan-Meier curves and descriptive statistics will be used to summarize first respiratory-related hospitalization. Log-rank test will be used for comparing treatment difference. BSC patients will be censored on cross over.

3.7.2.11 Time to respiratory-related death

Kaplan-Meier curves and descriptive statistics will be used to summarize respiratory-related death. Log-rank test will be used for comparing treatment difference. BSC patients will be censored on cross over.

3.7.2.12 SGRQ

Descriptive statistics (n, mean, std, median, min, max) of SGRQ scores on baseline, week 12, 24, 48 and 96 and change from baseline will be summarized by treatment group.

3.7.3 Exploratory Endpoints

Descriptive statistics (n, mean, std, median, min, max) of MMP7, CCL18 and SPD will be tabulated by treatment group and study visit.

3.8 Safety Analysis

Safety assessments include AEs, serious adverse events (SAEs), PEs, vital sign measurements, clinical laboratory evaluations, ECGs, and reasons for treatment discontinuation due to toxicity.

3.8.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 20.0 or greater). The number and percentages of subjects experiencing treatment-emergent AEs will be tabulated by system-organ class and preferred term and will be presented by treatment group. The number of events by preferred term will also be summarized. Tabulation by maximum severity and relationship to KD025 will also be included by treatment group. Summary subject listing will be provided for SAEs, AEs resulting in study discontinuation and deaths. All AEs (including SAEs will be graded using a 5-point scale (mild, moderate, severe, life threatening, or death).

Treatment emergent adverse events (TEAEs) are any adverse events occurring or worsening in severity after the first administration of study medication or randomization (for BSC patients). The TEAE incidence will be presented by treatment group.

The number and percentage of patients who experienced at least one TEAE as well as the number and percentage of patients who experienced each specific system organ class (SOC) and preferred term (PT) will be presented. For the presentation of AE incidences, the SOCs will be sorted alphabetically, and within SOC, the PT will be used and presented by decreasing total frequency. Separate tables will be provided for patients with adverse events occurring with an incidence in preferred term greater than 5% (in at least one treatment arm) and presented by decreasing total frequency,

TEAEs, SAEs, related TEAEs, related SAEs, ≥ Grade 3 TEAEs, related ≥ Grade 3 TEAEs, and TEAEs leading to withdrawal and treatment discontinuation will be summarized according to treatment group, system-organ-class, and preferred terms.

AEs will also be presented in listings. Duration of AEs will be determined and included in listings, along with action taken and outcome.

The AE summaries will be presented for the 24 week Treatment Period as well as the entire treatment duration.

3.8.2 Clinical Laboratory Evaluation

The summary statistics (including number, mean, standard deviation, 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), hemoglobin, platelets, ALP, ALT, aspartate aminotransaminase, gamma glutamyl transferase, total bilirubin, glomerular filtration rate, plots of mean/mean changes from baseline with the corresponding standard error will be displayed.

Laboratory results will be classified using the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (as described in study Appendix A) and summarized by treatment group. Incidence of laboratory abnormalities will be summarized by treatment group. The worst on-study grade after the first dose of study drug will be summarized (or after Week 1, Day 1 visit for BSC cohort).

The incidence of ≥ Grade 3 laboratory abnormalities under treatment and shifts in toxicity grading from baseline to highest grade post-baseline will be displayed for both the 24 week Treatment Period and the entire study duration.

Summaries of the observed and change from baseline values at each scheduled assessment time-point will also be presented.

3.8.3 Vital Signs and Other Physical Findings

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

3.8.4 ECG

Descriptive statistics for ECG parameters (i.e., heart rate (HR), PR interval, RR interval, QRS interval, QT interval, and QTcF interval) at each scheduled assessment time point will be presented for the values and change from baseline scores (note: Fridericia's correction: $QTcF = QT/RR^{(1/3)}$).

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

- < 450 msec
- 450 to 500 msec
- > 500 msec.

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 msec
- >0 to ≤ 30 msec
- >30 to ≤ 60 msec
- > 60 msec.

The 2 analyses will also be repeated using QT instead of QTcF.

3.8.5 Physical Examination

The complete set physical examination findings will be provided in listings. Clinically significant physical examination abnormalities will be included and summarized as AEs if appropriate.

4 List of Tables, Figures and Listings

Table 2 lists demographic and baseline characteristics TLFs; Table 3 lists treatment exposure and concomitant medication TLFs; Table 4 lists efficacy TLFs; and Table 5 lists safety TLFs.

Table 2. Demographics and Baseline Characteristics TLFs

T/F/L	Title	Population
T	Patient disposition and analysis population	All randomized patients
L	Patient disposition	mITT
L	Protocol deviations	All randomized patients
T	Demographics	mITT
L	Demographics and baseline characteristics	mITT
T	Medical history	mITT
L	Medical history	mITT
T	IPF history	mITT
L	IPF history	mITT
T	Prior medications	mITT

Table 3. Treatment Exposure and Concomitant Medication TLFs

T/F/L	Title	Population
T	Concomitant medications	mITT
L	Concomitant medications	mITT
T	Treatment exposure and compliance - 24 week treatment period	mITT
L	Treatment exposure and compliance	mITT

T/F/L	Title	Population
T	Dose modifications - 24 week treatment period	mITT
L	Dose modifications	mITT
T	Treatment exposure and compliance - entire treatment duration	mITT
T	Dose modifications - entire treatment duration	mITT

Table 4. Efficacy TLFs

T/F/L	Title	Population
T	24 week change from baseline on FVC (ml)	mITT
T	24 week change from baseline on FVC % of predicted value	mITT
T	48, 72, 96 week change from baseline on FVC (ml)	mITT
T	48, 72, 96 week change from baseline on FVC % of predicted value	mITT
T	FVC % predicted value decrease from baseline >=5% within 24 weeks	mITT
T	FVC % predicted value decrease from baseline >=10% within 24 weeks	mITT
T	FVC % predicted value decrease from baseline >=5% within 48, 72, 96 weeks	mITT
T	FVC % predicted value decrease from baseline >=10% within 48, 72, 96 weeks	mITT
T	Change from baseline on FVC (ml)	mITT
F	Mean (SD) Profiles for FVC (ml) change from baseline by group - Linear scale	mITT
T	Change from baseline on FVC % of predicted value	mITT
F	Mean (SD) Profiles for FVC % of predicted value change from baseline by group - Linear scale	mITT
T	24 week change from baseline on 6MWD	mITT
T	48, 72, 96 week change from baseline on 6MWD	mITT
T	6MWD decrease >=50 meters within 24 weeks	mITT
T	6MWD decrease >=50 meters within 48, 72, 96 weeks	mITT
T	Change from baseline on 6MWD	mITT
F	Mean (SD) Profiles for 6MWD change from baseline by group - Linear scale	mITT
T	24 week change from baseline on Dlco (%)	mITT
T	48, 72, 96 week change from baseline on Dlco (%)	mITT
T	24 week change from baseline on Dlco (%) <= -15%	mITT
T	48, 72, 96 week change from baseline on Dlco (%) <= -15%	mITT
T	Change from baseline on Dlco (%)	mITT
F	Mean (SD) Profiles for DLco (%) change from baseline by group - Linear scale	mITT
L	Efficacy measurements	mITT
T	Time to acute exacerbation of IPF	mITT
F	Kaplan Meier Plot of Time to acute exacerbation of IPF	mITT
T	Time to IPF progression	mITT

T/F/L	Title	Population
T	Time to first respiratory-related hospitalization	mITT
F	Kaplan Meier Plot of Time to first respiratory-related hospitalization	mITT
T	Time to respiratory-related death	mITT
F	Kaplan Meier Plot of Time to respiratory-related death	mITT
L	Time to event endpoints	mITT
T	Change from baseline on lung fibrosis (HRCT)	mITT
F	Mean (SD) Profiles for lung fibrosis (HRCT) change from baseline by group - Linear scale	mITT
T	Change from baseline on SGRQ score	mITT
F	Mean (SD) Profiles for SGRQ score change from baseline by group - Linear scale	mITT
T	Change from baseline on MMP7 (ug/L)	mITT
F	Mean (SD) Concentration Profiles for MMP7 (ug/L) change from baseline by group - Linear scale	mITT
T	Change from baseline on CCL18 (ng/L)	mITT
F	Mean (SD) Concentration Profiles for CCL18 (ng/L) change from baseline by group - Linear scale	mITT
T	Change from baseline on SPD (ug/L)	mITT
F	Mean (SD) Concentration Profiles for SPD (ug/L) change from baseline by group - Linear scale	mITT

Table 5. Safety TLFs

T/F/L	Title	Population
T	Overall summary of TEAEs - 24 week treatment period	Safety
T	TEAEs by SOC and PT - 24 week treatment period	Safety
T	Serious TEAEs by SOC and PT - 24 week treatment period	Safety
T	Related TEAEs by SOC and PT - 24 week treatment period	Safety
T	Related Serious TEAEs by SOC and PT - 24 week treatment period	Safety
T	Grade 3 and 4 TEAEs by SOC and PT - 24 week treatment period	Safety
T	Related Grade 3 and 4 TEAEs by SOC and PT - 24 week treatment period	Safety
T	TEAEs leading to treatment discontinuation by SOC and PT - 24 week treatment period	Safety
T	Related TEAEs leading to treatment discontinuation by SOC and PT - 24 week treatment period	Safety
T	Related TEAEs occuring in >=1% patients by PT - 24 week treatment period	Safety
T	TEAEs occuring in >=5% patients by PT - 24 week treatment period	Safety
T	TEAEs by PT and maximum severity - 24 week treatment period	Safety
L	Overall summary of TEAEs - entire treatment duration	Safety
T	TEAEs by SOC and PT - entire treatment duration	Safety
T	Serious TEAEs by SOC and PT - entire treatment duration	Safety

T/F/L	Title	Population
T	Related TEAEs by SOC and PT - entire treatment duration	Safety
T	Related Serious TEAEs by SOC and PT - entire treatment duration	Safety
T	Grade 3 and 4 TEAEs by SOC and PT - entire treatment duration	Safety
T	Related Grade 3 and 4 TEAEs by SOC and PT - entire treatment duration	Safety
T	TEAEs leading to treatment discontinuation by SOC and PT - entire treatment duration	Safety
T	Related TEAEs leading to treatment discontinuation by SOC and PT - entire treatment duration	Safety
T	Related TEAEs occuring in >=1% patients by PT - entire treatment duration	Safety
T	TEAEs occuring in >=5% patients by PT - entire treatment duration	Safety
T	TEAEs by PT and maximum severity - entire treatment duration	Safety
L	Adverse events	Safety
L	Serious Adverse events	Safety
L	Grade 3 and 4 Adverse events	Safety
L	Death	Safety
T	Change from baseline on lab values	Safety
T	Shifts in toxicity grading from baseline to highest grade post-baseline of laboratory abnormalities - 24 week treatment perio	Safety
T	Shifts in toxicity grading from baseline to highest grade post-baseline of laboratory abnormalities - entire treatment duration	Safety
L	Lab values with CTC grade >= 3	Safety
T	Change from baseline on vital signs	Safety
L	Vital signs	Safety
T	Change from baseline on ECG parameters	Safety
T	QTcF abnormalities	Safety
L	ECG values	Safety

Appendix A: Tables for Grading Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Grading of Liver-Related Laboratory Abnormalities				
FEATURE	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ALT	> ULN-3.0 ULN	> 3.0-5.0 ULN	> 5.0-20 ULN	> 20 ULN
AST	> ULN-3.0 ULN	> 3.0-5.0 ULN	> 3.0-10 ULN	> 10 ULN
Alkaline Phosphatase	> ULN - 2.5 × ULN	> 2.5 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20 ULN
GGT	> ULN - 2.5 × ULN	> 2.5 - 5.0 × ULN	> 5.0 - 20.0 × ULN	> 20 × ULN
Bilirubin	> ULN - 1.5 × ULN	> 1.5 - 3.0 × ULN	> 3.0 - 10.0 × ULN	> 10.0 × ULN

ALT = Alanine aminotransferase; AST = aspartate aminotransferase; GGT = Gamma-glutamyl transferase; ULN = upper limit of normal

Chemistry*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma

Chemistry*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 × ULN***	1.6 – 3.0 × ULN	3.1 –10 × ULN	> 10 × ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 × ULN	1.6 – 2.0 × ULN	2.1 – 5.0 × ULN	> 5.0 × ULN

The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a Grade 3 parameter (125-129 mEq/L) should be recorded as a Grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***"ULN" is the upper limit of the normal range.

Hematology *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from Baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from Baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 × ULN**	1.11 – 1.20 × ULN	1.21 – 1.25 × ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 × ULN	1.21 – 1.4 × ULN	1.41 – 1.5 × ULN	> 1.5 × ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field	1 – 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Abstracted from: Food and Drug Administration (FDA). Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. US Department of Health and Human Services, Center for Biologics Evaluation and Research. September 2007.

Appendix B: References

1. American Thoracic Society, St. George's Respiratory Questionnaire (SGRQ) (https://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/sgrq.php)
2. Jones PW and the Nedocromil Sodium Quality of Life Study Group. Quality of life, symptoms, and pulmonary function in asthma: long-term treatment with nedocromil sodium examined in a controlled multicentre trial. Eur Respir J 1994, 7:55-62.
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