STATISTICAL ANALYSIS PLAN (SAP)

A Randomized, Placebo-Controlled, Double-Blind Six-Month Study Followed by an Open-Label Extension Phase to Evaluate the Efficacy, Safety and Tolerability of MN-001 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

Protocol Version: Amendment 1 (15 April 2015)

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07 April 2021	**1.0**

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1. HISTORY OF CHANGES

All versions of the document have to be documented in the table of history of changes. The owner of the document has to act in accordance with the latest version of the document.

Status	Version	Effective Date	Change description
New	*1.0*	**07 April 2021**	*None: Initial Document*

2. ABBREVIATIONS

Acronyms, Abbreviations, Initials	Description / Explanation
ACC	*Accelsiors CRO and Consultancy Services*
AE	*Adverse Event*
ATAQ-IPF	*A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis*
BS	*Biostatistics*
Cfb	*Change from baseline*
CRF	*Case Report Form*
Core Review Team	*Consists of Project Manager, Head of Drug Safety Unit, Clinical Data Manager, Biostatistician*
CSR	*Clinical Study Report*
DM	*Data Management*
DMP	*Data Management Plan*
DBT Phase	*Double-Blind Treatment Phase*
FAS	*Full Analysis Set*
FDA	*United States Food and Drug Administration*
FVC	*Forced Vital Capacity*
GCP	*Good Clinical Practice*
ICH	*The International Concil for Harmonization of Technical Requirements for Pharmaceuticals for Human Use*
IPF	*Idiopathic Pulmonary Fibrosis*
NA	*Not Applicable*
MMRC	*Modified Medical Research Council Dyspnea Score*

Acronyms, Abbreviations, Initials	Description / Explanation
OLE Phase	*Open-Label Extension Phase*
QA	*Quality Assurance*
QC	*Quality Control*
QOL	*Quality of Life*
PM	*Project Manager*
RA	*Regulatory Authority*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SAS	*Safety Analysis Set*
SOP	*Standard Operating Procedure*
TESAE	*Treatment Emergent Serious Adverse Event*
TEAE	*Treatment Emergent Adverse Event*
6MWT	6-minute walk test

3. General

Statistical Analysis Plan is an Accelsiors confidential document. The final approval of this SAP (by the Sponsor and Accelsiors) will occur prior to the unblinding of study treatment codes.

3.1. Scope

This SAP applies to all planned statistical analyses performed by Accelsiors Biostatistics.

Activity/Task	*Sponsor/ 3rd Party Vendor*	*ACC*	*N/A*
Final statistical analyses		x	

3.2. Purpose

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol *MN-001-IPF-201.* The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analysis not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analysis not identified in this SAP performed will be clearly identified in the respective CSR.

3.3. Preparation, Review and Changes to the SAP

The final draft version of SAP will be prepared by ACC project statistician for submission to *MediciNova Inc.* for review and input.

3.4. Changes to the Protocol

In case the clinical study protocol undergoes a major amendment affecting statistical analyses procedures, a new version of the SAP is issued.

4. PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting MediciNova Inc. protocol *MN-001-IPF-201 (A Randomized, Placebo-Controlled, Double-Blind Six-Month Study Followed by an Open-Label Extension Phase to Evaluate the Efficacy, Safety and Tolerability of MN-001 in Subjects with Idiopathic Pulmonary Fibrosis (IPF)).* This phase *2a* study is being completed to assess the *safety, tolerability, and efficacy* of *MN-001* for the treatment of *IPF* in *male and female subjects ≥ 21 and ≤ 80 years of age with a confirmed diagnosis of moderate to severe IPF.* The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol *MN-001-IPF-201* and amendment 1 issued *15APR2015.*
- Case report forms (CRFs) for Protocol *MN-001-IPF-201.*
- ICH E9: Guidance on Statistical Principles for Clinical Trials.
- ICH E3: Guideline for the format and content of the clinical and statistical sections of an application
- ICH E14: Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

5.1.1. Primary Objective

The primary objectives of the study are to evaluate:

- The effect of MN-001 in subjects with idiopathic pulmonary fibrosis (IPF) on the absolute and relative change from baseline of FVC and FVC % predicted up to 26 weeks
- The effect of MN-001 in subjects with idiopathic pulmonary fibrosis (IPF) on the semiannual rate of decline of disease activity based on forced vital capacity (FVC)

5.1.2. Secondary Objectives

The secondary objectives are to evaluate:

- The safety and tolerability of MN-001 in subjects with (IPF)
- Semiannual /Annual decline in disease activity based on the 6-minute walk test (6MWT)
- Change from baseline in disease activity based on Modified Medical Research Council Dyspnea Score (MMRC)
- Change from baseline in quality of life (QOL) measured by A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF)
- Frequency of worsening of IPF
- Time to first worsening of IPF

5.2. Study Endpoints (Outcome Variables)

5.2.1. Primary Outcome Variable(s)

To address the primary objective of the study the effect of MN-001 750mg will be evaluated based on the following clinical measures:

- absolute and relative change from baseline in FVC up to 26 weeks
- absolute and relative change from baseline in FVC % predicted up to 26 weeks
- semiannual rate of decline of disease activity based on forced vital capacity (FVC)

Forced vital capacity (FVC) is an index of respiratory function measured by a spirometry and an established measure of pulmonary function in IPF subjects. FVC is the volume of air that can forcibly

be blown out after full inspiration measured in liters. Spirometry assessments will be collected at the following time-points: Screening (Day -7), Double-Blind Treatment Period (Month 3 and Month 6), Open Label Extension Period (Month 9 and Month 12).

There can be five measurements of FVC and FVC% predicted at each visit for a subject. For each subject, the highest FVC and FVC% predicted measurements will be selected for analysis. The highest FVC and FVC% predicted measurements will be selected independently, meaning that the measurements can originate from different trials.

5.2.2. Secondary Outcome Variable(s)

- Semiannual/Annual rate of decline in disease activity based on the 6-minute walk test (6MWT):

  - Change in 6MWT distance

- Change from baseline in disease activity based on Modified Medical Research Council Dyspnea Score (MMRC):

  - MMRC score is a single score, assigned on a scale of 5 levels (0 [best] to 4 [worst])

- Change from baseline in quality of life (QOL) measured by A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF):

  - The ATAQ-IPF questionnaire has 13 domains (*Cough, Dyspnea, Forethought, Sleep, Mortality, Exhaustion, Emotional Well-being, Social Participation, Finances, Independence, Sexual Health, Relationships, Therapy*). The domain scores and *Total score* from these domain scores are calculated by summation. Higher scores correspond to greater impairment.
  - For statistical analysis, the *Total score* will be used as outcome variable which ranges from 74 to 370.

- Frequency of worsening IPF

  - Worsening of IPF is defined as:
    - acute IPF exacerbation
    - hospitalization due to respiratory symptoms
    - IPF related fatal events
    - lung transplantation

- Time to first worsening of IPF

Safety will be assessed by the proportion of subjects with the following events:

- Clinical and laboratory treatment emergent adverse events (TEAEs)
- Discontinuations due to TEAEs
- Treatment emergent serious adverse events (TESAEs)

Safety (relationship and severity of AEs) and tolerability will further be assessed by statistical and clinical review of AEs, laboratory values, ECGs, physical examinations, vital signs and weight.

6. STUDY METHODS

6.1. Overall Study Design and Plan

This is a randomized, placebo-controlled, double-blind 6-month study followed by a 6-month open-label extension phase to evaluate the efficacy, safety, and tolerability of MN-001 in moderate to severe IPF patients. MN-001 750 mg or matching Placebo will be orally administered twice daily over a 26-week period in subjects with a confirmed diagnosis of moderate to severe IPF per the ATS 2011 Guidelines (Raghu et al, 2011).

Approximately 15 subjects are planned to be enrolled. This study will consist of two treatment arms, MN-001 and matching Placebo. Randomization will occur in a 2:1 ratio (MN-001:Placebo). Eligible subjects will consist of males and females ranging in age from 21 to 80 years old, inclusive. The study will consist of a Screening Phase (up to 3 months prior to Day 1) followed by a 26-week double-blind Treatment Phase, a 26 week Open-Label Extension (OLE) phase and a Follow-up Visit (within 4 weeks after the last dose).

Overall study design and plan is described in detail in Final Protocol Amendment 1, Section 6. Overall Study Design and plan: Description.

6.2. Selection of Study Population

Inclusion and exclusion criteria are described in detail in Final Protocol Amendment 1, Section 7.2.

6.3. Method of Treatment Assignment and Randomization

During the Double-Blind Treatment Phase, randomization occured in a 2:1 ratio (MN-001:Placebo). The randomization scheme was generated by an independent statistician and sent to each site's unblinded pharmacist in a sealed envelope.

6.4. Treatment Masking (Blinding)

Subjects and all personnel involved with the conduct and interpretation of the study, including the investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor and accessible only to authorized persons (e.g., unblinded independent safety monitor) until the database is locked.

To ensure that treatment allocation remains concealed to both staff and participants, the following measures will be taken:

- Active drug and placebo will be identical in appearance
- Drug supplies to investigational pharmacy will be coded

7. SEQUENCE OF PLANNED ANALYSIS

7.1. Interim Analysis

There are no planned Interim Analyses for this study.

7.2. Data Monitoring Committee Meetings

Not applicable.

8. SAMPLE SIZE DETERMINATION

No prior data are available on which to base assumptions for sample size/power considerations. The results of this pilot study will be used to design future studies, and the sample size of approximately 15 subjects is deemed to be appropriate for this purpose.

9. ANALYSIS POPULATIONS

The following analysis populations are planned for the studies:

- **Full Analysis Set (FAS)** will include all enrolled subjects who receive at least one dose of study medication and have at least one post efficacy assessment.

- **Safety Analysis Set (SAS)** will include all subjects who received at least one dose of study drug and had at least one post dose safety assessment.

9.1. Use of analysis populations in different analyses

Safety analyses will be conducted on the Safety Analysis Set, and subjects will be analyzed based on the treatment they received. Efficacy analysis will be conducted on the Full Analysis Set, and subjects will be analyzed based on the treatment to which they were randomized.

10. GENERAL ISSUES FOR STATISTICAL ANALYSIS

Data from all clinical assessments will be listed and, where appropriate, summarized by treatment arms using descriptive statistics. Summary (descriptive) statistics of continuous variables include n, mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum values at each time-point. For categorical variables, the number and percent of counts will be presented.

10.1. Definition of Treatment Arms

Treatment arms will be denoted as follows in the TLFs:

- "MN-001" - 750 mg of MN-001 administered orally twice daily
- "Placebo" – Matching Placebo administered orally twice daily
- "Former Placebo" – Matching Placebo administered orally twice daily during the Double-Blind Treatment Phase and 750 mg of MN-001 administered orally twice daily during the OLE Phase

10.2. Definition of Study Phases

- **Double Blind Treatment Phase (DBT Phase)**

  The DBT Phase starts with Visit 3 which is the Day 1 of the DBT phase.

  The DBT Phase ends with end of the day of Visit 8 (Month 6) and assessments taken on this visit will be considered as belonging to the DBT phase.

- **Open Label Extension Phase (OLE Phase)**

  The OLE Phase starts on the following day of Visit 8 and ends with Visit 14(Month 13).

10.3. Definition of Baseline

Unless otherwise specified, baseline is defined as the measurement closest to the date of the first administration of Investigational Medicinal Product (IMP), and preceding the first dose of IMP (MN-001 or Placebo).

For the DBT Phase, baseline values will be assessed pre-dose at Visit 3 (Day 1) in this study. For pulmonary function test, 6MWT, MMRC, ATAQ-IPF and 12-Lead ECG, the baseline values will be assessed at Visit 2 (Day -7).

For the OLE Phase, unless otherwise specified, baseline values for those subjects who were taking Placebo in the DBT Phase will be defined as measurements closest to the first administration of MN-001 and preceding the first dose of MN-001. Therefore, these baseline values will be the ones assessed pre-dose on Visit 8 (Month 6) of the DBT phase.

10.4. Definition of Visit Windows

The same visit windows will be used as defined in the protocol.

10.5. Multicentre Studies

This is a single-center study.

10.6. Multiple Comparisons and Multiplicity

The results of all statistical tests (i.e., P values) will be interpreted descriptively, and no adjustment for multiple comparisons will be made.

10.7. Planned Subgroup Analyses

No subgroup analyses are planned in this study.

10.8. Analysis Software

All analysis will be performed using SAS® Software version 9.4 or above.

11. STUDY SUBJECTS

11.1. Disposition of Subjects and Withdrawals

All subjects who provide informed consent will be accounted for in this study. The number of screen failures will be presented. The number and proportion of subjects in each analysis set will be presented by treatment arm (in percentage of the number of subjects randomized) and overall. The number and

proportion of completers will be presented by treatment arm and overall. The number and proportion of early withdrawals will be presented by the coded term for main reason of withdrawal and overall, by treatment arm and overall.

Subjects who are in the Safety Analysis Set but not in the Full Analysis Set will be listed.

Randomization errors will be listed.

11.2. Protocol Deviations

The number and proportion of subjects with protocol deviations will be presented by treatment arm, for each coded term.

All protocol deviations will be listed.

11.3. Inclusion and Exclusion Criteria

Subjects who meet all the inclusion criteria and none of the exclusion criteria are eligible to participate in the clinical trial.

Deviations from inclusion/exclusion criteria will be listed.

12. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

12.1. Demographics

For variables assumed to be continuous, like age at screening, body weight and height descriptive statistics will be prepared by treatment arm, for each analysis set separately.

For categorical variables like gender, race, ethnicity, frequency tables (n and percentage) will be prepared by treatment arm, for each analysis set separately.

All demography data will be listed.

12.2. Prior and Concomitant Medications

Prior medications/therapies are defined as those for which the end date is prior to the date of first IMP administration. Concomitant medications/therapies are defined as those with start date on or after the date of first IMP administration and those with start date prior to the first IMP use but with end date on or after the date of first IMP administration.

Concomitant medications entered into the database will be coded using the most recent version of the World Health Organization Drug Dictionary which employs the Anatomical Therapeutic Chemical (ATC) classification system. The number and percentage of subjects who took prior and concomitant medications will be summarized separately by ATC classification first level (alphabetically), ATC classification second level (in decreasing order of frequency) and treatment arm.

These therapeutics will be listed by subject along with their classification, indication of the treatment, total daily dose and start and stop date of the treatment.

The number and percentage of subjects who took prior and concomitant treatments will be presented separately.

All prior and concomitant medication data will be listed.

12.3. Baseline and Screening Conditions

Baseline and Screening condition data will be assessed by treatment arm using descriptive statistics. No inferential test statistics are planned for baseline comparison of the treatment arms.

12.3.1. Baseline Medical History

All medical history events and their details will be listed. The number and percentage of subjects in different medical history categories will be presented by treatment arm.

12.4. Measurement of Treatment Compliance

Number of prescribed and taken capsules will be calculated and listed.

Compliance will be assessed by counting capsules and dividing the actual number of doses taken (per capsule count) by the number of doses the subject should have taken within a visit period and multiplying by 100.

Subjects who miss more than 25% of scheduled doses or take more than 125% of the scheduled doses will be considered noncompliant and may be discontinued from the study per investigator's judgment.

Descriptive statistics for treatment compliance will be provided. Number of subjects with low compliance (<75%) and with too high compliance (>125%) will be presented by treatment arm.

Start date of the dosing period, dose, dosing frequency and number of dosing days will be listed.

13. EFFICACY ANALYSIS

Efficacy analysis will be performed on the Full Analysis Set. All efficacy measurements will be listed.

13.1. Primary Efficacy Variable Analysis(s)

The primary efficacy endpoints are the absolute and relative change from baseline in FVC and FVC% predicted up to 26 weeks, and the semiannual decline of disease activity based on FVC. To estimate the semiannualized rate of change in FVC between baseline and Month 6, a random intercept, random slope linear mixed model will be fitted (using proc mixed in SAS). Missing data will not be imputed because the ML-estimate is unbiased for this model in case of a Missing at Random (MAR) mechanism.

The model equation is the following:

$$Y_{ij} = \alpha + \beta_1 t_{ij} x_{1i} + \beta_2 t_{ij} x_{2i} + a_i + b_i t_{ij} + \varepsilon_{ij}$$

where:

Y_{ij} is the FVC value for the ith subject at the jth time point

α is the common intercept

t_{ij} denotes time point *j* for the ith subject (actual time in half-years)

x_{1i} = 1 if subject *i* is in the active treatment arm, and 0 otherwise

x_{2i} = 1 if the subject *i* is in the placebo arm, and 0 otherwise

a_i and b_i are random effects (random intercepts and slopes) for subject *i*

ε_{ij} is a random error term

The following null hypothesis (equal mean rates of change) will be tested within this model:

$H_0: \beta_1 = \beta_2$

The alternative hypothesis is:

$H_1: \beta_1 \neq \beta_2$

This hypothesis will be tested at a two-sided 0.05 level.

To measure time in half-years the following formula will be used:

$$number\ of\ study\ days * \left(\frac{2}{365.25}\right)$$

All efficacy measurements will be listed.

Descriptive statistics of actual values, changes from baseline and relative changes from baseline will be provided for FVC and FVC % predicted by treatment arm and visit. Descriptive statistics and listing of the estimated semiannual FVC rates of change will be provided as well.

To assess the effect of MN-001 as compared to Placebo based on FVC, change from baseline to Month 3 and change from baseline to Month 6 will be analysed within an analysis of covariance (ANCOVA) model respectively, with treatment as a fixed effect and baseline FVC as covariate. Least-squares means (LSM) for the change from baseline to Month 3 and Month 6 will be provided, including 95% CIs.

The same analysis will be repeated for FVC % predicted.

The analysis will be performed on the Full Analysis Set (FAS).

13.2. Sensitivity and Supportive Analyses for the Primary Efficacy Variable(s)

As a sensitivity analysis, the analysis of Primary Efficacy Variables will be repeated on two subsets of subjects:

- subjects with no major protocol deviations or protocol exemption

- subjects who are valid completers (ie. subjects who were compliant with the protocol and completed the Double-blind Treatment Period).

If a subset of subjects does not differ from FAS then the analysis will not be repeated for that subset.

13.3. Secondary Efficacy Variable Analysis

The secondary efficay endpoints are the following:

- Annual/semiannual decline on disease activity based in the 6-minute walk test (6MWT)
- Modified Medical Research Council Dyspnea Score (MMRC)
- Quality of life (QOL) measured by A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF)
- Frequency of worsening IPF
- Time to first worsening of IPF

Semiannual rate of change in 6MWT outcome (change in 6MWT distance) will be estimated using the same linear mixed model as for FVC. For estimating the annual rate of change in 6MWT outcomes, the t_{ij} covariate of this linear mixed model will be modified to measure time in years. For those subjects who were taking MN-001 during the DBT phase and OLE phase as well, semiannual rate of change will be estimated for the DBT phase and annual rate of change will be estimated for the DBT and OLE phases as a whole. For those subjects who were taking Placebo during the DBT phase and MN-001 during the OLE phase, semiannual rate of change will be estimated for the DBT phase and for the OLE phase respectively.

Descriptive statistics of estimated semiannual and annual 6MWT measurements will be provided by treatment arm and visit. Descriptive statistics will be provided of actual MMRC scores and ATAQ-IPF total scores as well as changes from baseline of these scores, by treatment arm and visit.

Number of events related to worsening IPF will be calculated by treatment arm and event category (acute IPF exacerbation, hospitalization due to respiratory symptoms, IPF related fatal events, lung transplantation). Number and proportion of subjects in different event categories will also be provided: a subject may be counted multiple times, but within each category will be counted only once.

For time to first worsening in IPF a Kaplan-Meier analysis will be performed, estimating the mean and median time to first worsening (and their 95% CI) for each treatment arm. Those subjects who do not experience any adverse event related to worsening in IPF until Month 6 will be censored at their last visit. The estimated survival functions will be presented graphically.

To test the equality of distributions of times to first IPF worsening in the two treatment arms, the Log-Rank test will be applied with the following null-hypothesis:

H_0: $S_{1t} = S_{2t}$ (the survival functions are identical in the two treatment arms)

The alternative hypothesis is:

H_1: $S_{1t} \neq S_{2t}$ (the survival functions are not identical)

This hypothesis will be tested at a two-sided 0.05 level.

The analysis will be performed on the Full Analysis Set (FAS).

13.4. Sensitivity and Supportive Analyses for the Secondary Efficacy Variable(s)

For those subset of subjects who were compliant with the protocol and completed the DBT and OLE Phases, the analysis of 6MWT will be repeated. If this subset of subjects does not differ from FAS then the analysis will not be repeated.

14. SAFETY AND TOLERABILITY ANALYSIS

All safety analyses will be performed for subjects in the safety analysis set.

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each subject:

- Treatment Emergent Adverse Events:
  - Clinical laboratory Treatment Emergent Adverse Events
  - Discontinuation due to TEAEs
  - Treatment Emergent Serious Adverse Events
- Pregnancies (if any reported)
- Clinical Laboratory Investigations
- Hemodynamics (vital signs)
- ECG Investigations
- Physical examinations
- Body weight

The analysis of safety assessments will be done for the DBT Phase and OLE Phase separately.

14.1. Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version *21.0*.

Summary tables for AEs will include treatment-emergent adverse events (TEAEs, defined as AEs occurred during or after the first administration of a study drug). AEs occurred before the first administration of a study drug will be listed separately. Aes occurring 7 days after the last dose of study medication will be listed separately.

Unless otherwise stated, AE analyses will be subject-based, each subject will be counted once in frequency tables at the subject, SOC and preferred term levels, and the denominator for percentages will be the number of subjects in the SAS, in the respective treatment arm (i.e. “as treated” assignment of treatment arms).

AEs will be assigned to study phases (DBT or OLE) based on their start date.

If the start date of an AE is incomplete:

a/ If only day is missing, and if in the same month the treatment was started then the start date of AE will be imputed with the day of first treatment. If treatment started earlier and not in that month then the first day of the month will be used for imputation.

b/ If month and day are missing, and the treatment start date was in the same year then the start date of AE will be imputed with the month and day of the first treatment administration. If the treatment start date was in the previous year, then 01 JAN will be used for imputation.

c/ If the entire AE start date is missing then the date will not be imputed, but the AE will be considered treatment-emergent.

If the end date of an AE is missing, the AE will be considered as ”ongoing”.

If a subject xperiences a TEAE with a missing causality assessment, then relationship will be categorized as “Related”. AEs with a missing causality assessment during the screening period relationship will be categorized as “Unrelated”.

If a subject experiences a TEAE with a missing severity assessment, then severity for this TEAE will be categorized as “Severe”.

In addition to keeping the 5-level categorization of causality of AEs, they will alsobe dichotomized into two categories: related/not related. “Related” category comprises events which were classified by the investigator as possibly, probably or related to treatment, whereas “Not Related” category comprises the other two levels of the investigator’s assessment (“Unlikely to be related” and “Unrelated”).

14.1.1. All Adverse Events

An overview of number of subjects (%) with treatment-emergent AEs will be presented for the main AE categories (All AEs, AEs leading to discontinuation, SAEs, SAEs leading to discontinuation, AEs with at least Grade 3 severity (Severe AEs, Life-threatening AEs, Deaths), AEs and SAEs with relationship to IMP as possibly related, probably related, or related) by treatment arm and phase.

The number (%) of subjects with treatment-emergent AEs will be presented by phase, treatment arm, System Organ Class and Preferred Term (MedDRA), AE severity, and relationship to study drug (for both AEs and SAEs). Each subject will be counted only once within each preferred term per study phase. If a subject experiences more than one AE within a preferred term for the same recording phase, only the AE with the strongest relationship or highest severity, as appropriate, will be included in the summaries by relationship and severity.

14.1.2. Adverse Events Leading to Withdrawal

A data listing of AEs leading to withdrawal will be provided, displaying details of the event(s) captured on the CRF.

14.1.3. Serious Adverse Events

A data listing of SAEs will be provided, displaying details of the event(s) captured on the CRF. Serious adverse event narratives will be provided for the CSR by MediciNova.

14.1.4. Deaths

If any subject dies during the study, relevant information will be supplied in a data listing, and appropriate SAE narratives.

14.2. Pregnancies

Pregnancy data will be shown in a data listing. No special analysis will be performed on the pregnancy data. Subjects are to be discontinued from the study if they become pregnant.

14.3. Clinical Laboratory Evaluations

For numerical lab measurements values below the lower detection limit or above the upper detection limit (indicated in the database as <xx, ≤ xx, >xx, ≥ xx) will be replaced by the detection limit (i.e. xx). Measurements resulting in negative numbers will be set to missing.

Descriptive statistics of measurements will be presented for clinical laboratory values, by treatment arm, phase and visit. Descriptive statistics of changes from baseline will be presented for clinical laboratory values, by treatment arm, phase, and visit.

Categorical lab measurements will be tabulated by treatment arm and visit.

Parameters will be grouped as:

- Blood Chemistry Tests
- Haematology tests
- Urinalysis Tests

Lab shift tables presenting the incidence of new or worsening clinically significant findings from baseline to the last visit will be displayed by treatment arm, for DBT and OLE phase respectivel. For this, a shift table will be created by phase, treatment arms and parameters with the following categories: “CS Low”, “NCS Low”, “Normal”, “NCS High”, “CS High”.

Shift from baseline to the highest lab value, and from baseline to the lowest lab value will also be displayed, for the DBT and OLE periods respectively. To create this shift table, change from baseline to the highest and lowest values will be calculated for every subjects within DBT and OLE periods, respectively. Descriptive statistics of these change from baseline values will be presented by phase, treatment arms, parameter and change from baseline category (Cfb to lowest, Cfb to highest). A by-subject listing of these change fom baseline values will be provided.

Incidence of out-of-normal-range values and markedly abnormal change from baseline in laboratory safety test variables will be tabulated by treatment arm and phase. A markedly abnormal change from baseline value is defined as any value larger than three times the upper normal limit.

Laboratory values that are outside the normal range, and their clinically significance will be flagged in the data listings. A by-subject listing of all subjects with abnormal laboratory values will be provided.

14.4. Hemodynamics (Vital Signs)

Descriptive statistics of actual values and changes from baseline will be calculated for SysBP, DiaBP, HR and Respiratory rate and Temperature. These summaries will be presented by treatment arm, phase and visit.

All vital sign measurements will be listed.

14.5. Body weight

For body weight, descriptive statistics will be prepared by treatment arm, phase, and visit.

All weight measurements will be listed.

14.6. ECGs

Descriptive statistics will be presented for ECG measures of PR interval, QRSD interval, QT interval, QTc interval (Fridericia's method), and HR. These statistics will be presented by treatment arm, phase and visit.

The number and percentage of subjects with normal and abnormal ECG results will be summarized by treatment arm, phase and visit. All ECG measurements will be listed.

14.7. Physical examination

Physical examination results will be summarized for each variable (Skin, HEENT, Lymph nodes, Neck and Thyroid, Breasts, Chest/Lungs, Heart, Vascular, Abdomen, Neurological, Extremities/Joints) by phase, visit, and treatment arm. All physical examination data together with evaluations will be listed, abnormal findings will be flagged.

15. Departures from Protocol

The protocol states that besides the change in 6MWT distance the following items will be measured for 6MWT:

- Change in 6MWT oxygen saturation area under the curve using the same oxygen dose as the baseline,
- Change in 6MWT minutes walked

However, there was no continuous SpO_2 measurement during the 6MWT test hence the area under the curve cannot be calculated. The second item was supposed to measure for how long a participant walked within the six minutes, but this information was not captured.

Therefore, these measurements are omitted from the secondary endpoints of the SAP.

The protocol defined TEAE definition (AEs occurring from the time of first dose through 7 days after the last dose of study medication) was changed.

16. LIST OF APPLICABLE QUALITY DOCUMENTS

16.1. List of Relevant SOPs and WINs

Document Code	Title	Effective Date
SOP-BS-005	*Statistical Analysis Plan*	
SOP-BS-008	*Statistical Analysis and Programming*	
WIN-BS-030	*Conventions for Statistical Programming*	

17. References

No.	Designation/ Code/Appendix	Title
1	*NA*	*ICH Harmonised tripartite Guideline: Guideline for Good Clinical Practice*
2	*NA*	*ICH Harmonised tripartite Guideline: STRUCTURE AND CONTENT OF CLINICAL STUDY REPORTS E3*
3	*NA*	*ICH Harmonised tripartite Guideline: STATISTICAL PRINCIPLES FOR CLINICAL TRIALS E9*
4		*ICH E14 Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs*
5	*NA*	*FDA-CDER: GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF AN APPLICATION*
		Raghu G, Collard HR, Egan JJ, et al. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Respir Crit Care Med 2011 Mar 15; 183(6):788-824.
Comments:		

18. Appendices

18.1. Appendix A / Schedule of Assessments

Phase	Screening		Double-Blind Treatment						Open-Label Extension					Follow-up End of Study	Early Termination[c]	Lab retest[f]
	Day -90 to -8	Day -7 (±5d)	Day 1	Week 1 (±3d)	Month 1 (±5d)	Month 3 (±5d)	Month 4 (±5d)	Month 6 (±5d)	Week 27 (±3d)	Month 7 (±5d)	Month 9 (±5d)	Month 10 (±5d)	Month 12 (±5d)	Month 13 (±5d)		
Visit Type	Clinic	Clinic	Clinic	Tel	Clinic	Clinic	Tel	Clinic	Tel	Clinic	Clinic	Tel	Clinic	Clinic		
Study Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	ET	LRT
Informed consent	X[a,b]	X[b]														
Inclusion/exclusion criteria review		X	X													
Medication history		X														
Physical Examination		X			X	X		X		X	X		X	X	X	
Body height		X														
Body weight		X			X	X		X		X	X		X	X	X	
Vital signs (sitting)		X	X		X	X		X		X	X		X	X	X	
12-lead ECG		X	X[g]		X	X		X		X	X		X		X[d]	
CBC/CMP, CK, UA Fasting lipid panel		X			X	X		X		X	X		X		X[d]	X
Serum pregnancy test		X														
Urine pregnancy test			X		X	X		X		X	X		X		X[d]	
Pulmonary function		X				X		X			X		X		X[d]	
6 minute-walk test		X				X		X			X		X		X[d]	
ATAQ-IPF		X				X		X			X		X		X[d]	
MMRC		X			X	X	X	X		X	X	X	X		X[d]	
Plasma for Biomarker		X						X					X		X[d]	
Adverse event review			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant med review			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing			X		X	X		X[e]		X	X		X			
Dispense/Review/ Collect Patient Diary			X		X	X		X		X	X		X		X	
Study Drug Accountability					X	X		X		X	X		X		X	

a. A copy of the informed consent form (ICF) will be given to the patient for review.
b. Signing of the ICF will occur during screening phase (Visit 1 or Visit 2) prior to conducting any study assessments.

c. Assessments to be done for early termination for any reason. Other assessments/procedures to be done at PI discretion, if necessary.
d. Assessments do not need to be performed if prior assessments were within one month of this early termination visit.
e. Dispense Open-label study medications after all procedures and assessments have been completed.
f. Lab retest assessments to be done for subjects with clinically significant abnormal lab findings.
g. 12-lead ECG to be done at Hour 1.5 (± 30 minutes) post dose

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