# Cover Page for SAP

| | |
|---|---|
| Sponsor name: | Novo Nordisk A/S |
| NCT number | NCT04764448 |
| Sponsor trial ID: | DCR-A1AT-201 |
| Official title of study: | A Phase 2, Randomized, Double-blind, Placebo-controlled Study Investigating Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Two Dose Levels of Belcesiran in Patients with Alpha-1 Antitrypsin Deficiency-Associated Liver Disease |
| Document date* | 20-May-2024 |

*Document date refers to the date on which the document was most recently updated.

[redacted]

# STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Protocol Title:** | A Phase 2, Randomized, Double-blind, Placebo-controlled, Study Investigating Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Study of Belcesiran in Patients with PiZZ Alpha-1 Antitrypsin Deficiency |
| **Protocol Number:** | DCR-A1AT-201 |
| **Protocol Version/Date:** | 1.0 / 03-Sep-2020<br>2.0 / 04-Feb-2021<br>3.0 / 08-Aug-2022 |
| **Investigational Product:** | Belcesiran, also known as DCR-A1AT |
| **Sponsor:** | Novo Nordisk Inc.<br>P.O. BOX 846<br>Plainsboro, NJ USA 08536 |
| **SAP Version/Date:** | 2.0 / 20-May-2024 |

[redacted]

[redacted]

*Redacted statistical analysis plan*
*Includes redaction of personal identifiable information only.*

# SIGNATURE PAGE

| | |
|---|---|
| **Protocol Title:** | A Phase 2, Randomized, Double-blind, Placebo-controlled, Study Investigating Safety, Tolerability, Pharmacokinetics and Pharmacodynamics Study of Two Dose Levels Belcesiran in Patients with Alpha-1 Antitrypsin Deficiency-Associated Liver Disease |
| **Protocol Number:** | DCR-A1AT-201 |
| **SAP Version/Date:** | 2.0/ 20-May-2024 |

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

| **Signature** | **Date** |
|---|---|
| [redacted]<br>*Electronically signed by: [redacted]*<br>*Reason: Approved*<br>*Date: May 20, 2024 17:10 EDT*<br>[redacted], [redacted]. | 20-May-2024 |
| [redacted]<br>*Electronically signed by: [redacted]*<br>*Reason: Approved*<br>*Date: May 21, 2024 09:16 EDT*<br>[redacted], ***Biostatistics***<br>***Novo Nordisk, Inc.*** | 21-May-2024 |
| [redacted]<br>*Electronically signed by: [redacted]*<br>*Reason: Approved*<br>*Date: May 21, 2024 12:12 EDT*<br>[redacted], [redacted]<br>***Novo Nordisk, Inc.*** | 21-May-2024 |

# VERSION HISTORY

| Version | Version Date | Description |
|---|---|---|
| 1.0 | 21-Mar-2024 | Original signed version |
| 2.0 | 20-May-2024 | Version 2.0 |

Below is a detailed summary of changes made in version 2.0 (20-May-2024) from version 1.0 (21-May-2024).

| Version | Section | Change* | Rationale |
|---|---|---|---|
| 2.0 | 3.3.2, 3.4.1 | Augmentation therapy inclusion | During the data cleaning process, the augmentation therapy was identified. |
| 2.0 | 3.7.2 | Analysis of the $FEV_1/FVC$ | The data was rejected due to a flow signal zeroing error. |
| | | | |

# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AAT | Alpha-1 antitrypsin |
| AATD | AAT deficiency |
| AATLD | alpha-1 antitrypsin deficiency-associated liver disease |
| ADaM | Analysis Data Model |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ATC | Anatomical therapeutic chemical |
| BMI | Body mass index |
| CDISC | Clinical Data Interchange Standards Consortium |
| F/U | Follow-up |
| CRF | Case report form |
| CRP | C-reactive protein |
| CSR | Clinical Study Report |
| DLCO | Diffusing capacity of the lungs for carbon monoxide |
| DSMC | Data Safety Monitoring Committee |
| ECG | Electrocardiogram |
| EOT | End of treatment |
| EOS | End of study |
| ET | Early termination |
| $FEV_1$ | Forced expiratory volume in one second |
| FVC | Forced vital capacity |
| IVRS/IWRS | Interactive Voice/Web Response System |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PD | Pharmacodynamic(s) |
| PE | Physical examination |
| PFT | Pulmonary function test(s) |
| PiZZ | Autosomal homozygous mutant AAT Z-allele genotype |
| PK | Pharmacokinetic(s) |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SD | Standard deviation |
| SDTM | Study Data Tabulation Model |
| SoA | Schedule of Activities |
| TEAE | Treatment-emergent adverse event |
| TFL | Tables, figures, listings |
| ULN | Upper limit of normal |
| WHO | World Health Organization |

# 1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of study data from protocol DCR-A1AT-201, "A *Phase 2, Randomized, Double-blind, Placebo-controlled Study Investigating Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Two Dose Levels of Belcesiran in Patients with Alpha-1 Antitrypsin Deficiency-Associated Liver Disease*". The SAP will be finalized prior to the final database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

The SAP reflects the planned study design as per the latest version of the protocol; however, the Sponsor made the decision to stop the trial prior to the enrollment of Cohort 3 subjects and prior to the completion of the planned study procedures for Cohorts 1 and 2 participants. Cohort 3 and related activity plan will be cancelled. Therefore, the available safety, AAT and biopsy data from Cohort 1 and Cohort 2 will be analyzed for the CSR purpose and there is no analysis planned for Cohort 3.

# 2 STUDY OVERVIEW

## 2.1 Study Objectives

### *2.1.1 Primary Objective*

The primary objectives are:

- To evaluate the safety and tolerability of multiple doses of belcesiran in patients with alpha-1 antitrypsin deficiency-associated liver disease (AATLD) for Cohorts 1 and 2.
- To characterize the pharmacodynamics (PD) of belcesiran in patients with AATLD for Cohorts 1, 2, and 3.

### *2.1.2 Secondary Objectives*

The secondary objectives are:

- To characterize the pharmacokinetics (PK) of belcesiran in the plasma of patients with AATLD.
- To assess the effect of belcesiran on liver histology in patients with AATLD.

### *2.1.3 Exploratory Objectives*

The exploratory objectives are:

- To assess the effect of belcesiran on liver stiffness in patients with AATLD.
- To assess the effect of belcesiran on liver fibrosis and/or inflammation in patients with AATLD.

## 2.2 Study Design

### *2.2.1 Overview*

The study is a multiple dose, randomized, placebo-controlled, double-blind study to evaluate the safety, tolerability, PK, and PD of 2 dose levels of belcesiran in adult patients with PiZZ AATLD (liver fibrosis F1, F2, F3, or F4, METAVIR scoring system).

After the screening period, Participants will be randomized, and administration of IMP (investigational medicinal product) will be initiated. Participants will return to the site for administration of IMP and safety, tolerability, PK, and PD monitoring at specified time points as per the schedule of activities (SoA) through the end of treatment (EOT) visit. If participants are not able to return to the site for assessments or

procedures, visits may be conducted by qualified medical professionals as at-home telemedicine and/or home nursing visits, at the discretion of the Investigator.

The study will be conducted in 3 separate cohorts. Participants will be randomized in a 1:1 fashion to either Cohort 1 or 2. Once Cohort 1 and 2 have enrolled, enrollment of Cohort 3 will be initiated.

- Participants in Cohort 1 (N=8) will be randomized 3:1 to either belcesiran 210 mg or placebo and a liver biopsy will be performed at week 24 to assess the effect of belcesiran. In addition, participants will have the option to continue treatment for an additional 72 weeks for a total treatment duration of 96 weeks.
- Participants in Cohort 2 (N=8) will be randomized 3:1 to either belcesiran 210 mg or placebo and a liver biopsy will be performed at week 48 to assess the effect of belcesiran. In addition, participants will have the option to continue treatment for an additional 48 weeks for a total treatment duration of 96 weeks.
- Participants in Cohort 3 (N=30) will be randomized 2:1:2:1 to belcesiran 210 mg, the equivalent amount of placebo for belcesiran 210 mg, belcesiran 50 mg or the equivalent amount of placebo for belcesiran 50 mg. Participants will be blinded within each dose level. Participants will have a liver biopsy performed at week 24 to assess the effect of belcesiran and thereafter continue treatment until 96 weeks of treatment have been completed.

Randomization will be stratified based on fibrosis stage (METAVIR Score F1/F2, F3 or F4) in all cohorts.

Participants in Cohort 1 and 3 will receive monthly dosing for the first 24 weeks and then shift to quarterly dosing thereafter until week 96. Participants in Cohort 2 will receive monthly dosing for the first 48 weeks and then shift to quarterly dosing thereafter until week 96. Participants will continue the IMP throughout the study, unless the participant or investigator decide to discontinue IMP, or the participant withdraws from the trial, or a discontinuation criterion is met.

All Participants in Cohorts 1 to 3 will have the option to undergo a liver biopsy at EOT/week 96. The biopsy at 96 weeks will inform about Z-AAT levels and provide further information about possible improvements in liver histology. Biopsy findings will be correlated with changes in non-invasive markers of liver disease and liver stiffness.

After the EOT visit, all participants will be followed up for 48 weeks. If a participant in Cohorts 1 and 2 does not wish to extend the treatment period to 96 weeks, they will proceed to the 48-week follow-up period instead.

The trial will be monitored by an independent external data safety monitoring committee (DSMC). The DSMC will review accumulating data from the trial in an unblinded fashion to ensure adequate monitoring of safety. The timing and scope of the review meetings will be defined in the DSMC charter.

Figure 1: Dose Regimens by Cohort

**Cohort 1**

| | Visit # | Dose # | Day | Week |
|---|---|---|---|---|
| Treatment Period | 1 | 1 | 1 | |
| | 2 | | 2 | |
| | 3 | | 3 | |
| | 4 | | 15 | |
| | 5 | 2 | 29 | |
| | 6 | | 30 | |
| | 7 | 3 | 57 | |
| | 8 | 4 | 85 | |
| | 9 | 5 | 113 | |
| | 10 | 6 | 141 | |
| | 11 | 7 | 169 | 24 |
| Optional Treatment Period | 12 | | 211* | |
| | 13 | 8 | 253 | |
| | 14 | | 295* | |
| | 15 | 9 | 337 | 48 |
| | 16 | 10 | 421 | |
| | 17 | 11 | 505 | 72 |
| | 18 | 12 | 589 | |
| | 19 | 13 | 673 | 96 |
| Follow-up Period | 18 | | 757 | |
| | 19 | | 841 | 120 |
| | 20 | | 925 | |
| | 21 | | 1009 | 144 |
| | 22 | | 1177 | |
| | 23 | | 1345 | 192 |

**Cohort 2**

| | Visit # | Dose # | Day | Week |
|---|---|---|---|---|
| Treatment Period | 1 | 1 | 1 | |
| | 2 | | 2 | |
| | 3 | | 3 | |
| | 4 | | 15 | |
| | 5 | 2 | 29 | |
| | 6 | | 30 | |
| | 7 | 3 | 57 | |
| | 8 | 4 | 85 | |
| | 9 | 5 | 113 | |
| | 10 | 6 | 141 | |
| | 11 | 7 | 169 | 24 |
| | 12 | 8 | 197 | |
| | 13 | 9 | 225 | |
| | 14 | 10 | 253 | |
| | 15 | 11 | 281 | |
| | 16 | 12 | 309 | |
| | 17 | 13 | 337 | 48 |
| Optional Treatment Period | 18 | 14 | 421 | |
| | 19 | 15 | 505 | 72 |
| | 20 | 16 | 589 | |
| | 21 | 17 | 673 | 96 |
| Follow-up Period | 22 | | 757 | |
| | 23 | | 841 | 120 |
| | 24 | | 925 | |
| | 25 | | 1009 | 144 |
| | 26 | | 1177 | |
| | 27 | | 1345 | 192 |

**Cohort 3**

| | Visit # | Dose # | Day | Week |
|---|---|---|---|---|
| Treatment Period | 1 | 1 | 1 | |
| | 2 | | 2 | |
| | 3 | | 3* | |
| | 4 | | 15* | |
| | 5 | 2 | 29 | |
| | 6 | | 30* | |
| | 7 | 3 | 57 | |
| | 8 | 4 | 85 | |
| | 9 | 5 | 113 | |
| | 10 | 6 | 141 | |
| | 11 | 7 | 169 | 24 |
| | 12 | | 211* | |
| | 13 | 8 | 253 | |
| | 14 | | 295* | |
| | 15 | 9 | 337 | 48 |
| | 16 | 10 | 421 | |
| | 17 | 11 | 505 | |
| | 18 | 12 | 589 | |
| | 19 | 13 | 673 | 96 |
| Follow-up Period | 20 | | 757 | |
| | 21 | | 841 | 120 |
| | 22 | | 925 | |
| | 23 | | 1009 | 144 |

Required Dosing Visits in yellow
Optional Dosing Visits in blue
Follow-up visits in gray
* Phone visit

### *2.2.2 Randomization and Blinding*

The study is a randomized, placebo-controlled, double-blind study, where the Investigator and the participants are blinded to IMP and placebo. All sites will have unblinded staff responsible for preparing IMP. A subset of the Sponsor's study team will be unblinded. Details of unblinding, including the list of unblinded Sponsor team members, will be captured in the Study Blinding Plan.

All participants will be centrally assigned to randomized study intervention using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, directions for the IWRS will be provided to each site.

Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, the unblinded site staff will be responsible for the preparation and dispensing of all study intervention and will endeavor to ensure that there are no differences in the time taken to dispense the study intervention following randomization. Additionally, the unblinded site staff will affix a translucent label over the syringe(s) to mask the contents.

The unblinded study monitor and any auditors present in the event of a Quality Assurance or a competent authority audit will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately and per protocol and the Pharmacy Manual.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, the Medical Monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation.

Potentially unblinding study results, such as the serum AAT protein concentrations, will not be shared with blinded study participants and site personnel during the treatment period.

Study intervention will be administered at the investigational site. The planned dose, actual administered dose, and injection date and time will be recorded on the appropriate electronic case report form (CRF).

### *2.2.3 Study Drug*

Belcesiran is supplied as a solution of the drug substance (belcesiran sodium) in water for injection.

### *2.2.4 Sample Size Determination*

The study will include 3 cohorts. In Cohorts 1 and 2 there will be up to 8 participants in each cohort (randomization scheme ratio of 3:1 active: placebo). The sample size for Cohort 1 and Cohort 2 is based on clinical consideration rather than statistical power calculation.

The primary endpoint for Cohort 3 of this study is the percentage change from baseline in serum and liver Z-AAT protein concentration at week 24. Assuming the percentage change from baseline is 80%, 60% and 10% in the active high dose group, active low dose group and placebo group respectively, and the standard deviation is 0.5 for all three groups, a sample size of 10 participants per treatment group will provide at least 80% power to detect a statistically significant difference between active high dose group and placebo, and between active low dose group and placebo, at an overall 1-sided significance level of 0.05.

The F1/F2, F3, and F4 fibrosis types will be used as randomization stratification factors for all 3 cohorts.

## 2.3 Study Endpoints

### *2.3.1 Primary Endpoints*

The primary endpoints for Cohorts 1 and 2 are:

- The incidence and nature of treatment emergent adverse events (TEAEs), and the change from Baseline in pulmonary function tests (PFTs), 12-lead electrocardiograms (ECGs), physical examination (PE) findings, vital signs, and clinical laboratory tests
- Changes from baseline to weeks 24 (Cohort 1)/ 48 (Cohort 2) in serum AAT protein concentrations

The primary endpoints for Cohort 3 are:

- Change from baseline to week 24 in serum AAT protein levels
- Change from baseline to week 24 in liver AAT protein levels

### *2.3.2 Secondary Endpoints*

The secondary endpoints are:

- PK profile of belcesiran
- Change from baseline up until week 96 in liver fibrosis
- Change from Baseline up until week 96 in diastase-resistant PAS-positive AAT globules

### *2.3.3 Exploratory Efficacy Endpoints*

The exploratory endpoints are:

- Change from Baseline up until week 96 in FibroScan® score
- Change from Baseline up until week 96 in enhanced liver fibrosis (ELF) score
- Change from Baseline up until week 96 in cytokeratin 18 (CK-18)

# 3 STATISTICAL METHODOLOGY

## 3.1 General Considerations

### *3.1.1 Analysis Day*

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. Note that for analysis purpose there will be no Day 0.

### *3.1.2 Analysis Visits*

Scheduled visits will be assigned to analysis visits as recorded on the CRF. Unscheduled visits recorded on the CRF will not be re-assigned and will remain labeled as unscheduled.

Early termination (ET) visits for Cohort 1 participants will be assigned to analysis visits according to the following visit windows if participants enter the optional treatment period:

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Screening | -35 | | -1 |
| Day 1 | 1 | 1 | 1 |
| Day 2 | 2 | 2 | 2 |
| Day 3 | 3 | 3 | 9 |
| Day 15 | 15 | 10 | 22 |
| Day 29 | 29* | 23 | 43 |
| Day 57 | 57 | 44 | 71 |
| Day 85 | 85 | 72 | 99 |
| Day 113 | 113 | 100 | 127 |
| Day 141 | 141 | 128 | 155 |
| Day 169 | 169 | 156 | 183 |
| Day 211 | 211 | 184 | 232 |
| Day 253 | 253 | 233 | 274 |
| Day 295 | 295 | 275 | 316 |
| Day 337 | 337 | 317 | 379 |
| Day 421 | 421 | 380 | 463 |
| Day 505 | 505 | 464 | 547 |
| Day 589 | 589 | 548 | 631 |
| Day 673 | 673 | 632 | 715 |
| Day 757- Post EOT Week 12 | 757 | 716 | 799 |
| Day 841-Post EOT Week 24 | 841 | 800 | 883 |
| Day 925- Post EOT Week 36 | 925 | 884 | 967 |
| Day 1009- Post EOT Week 48 | 1009 | 968 | 1093 |
| Day 1177- Post EOT Week 72 | 1177 | 1094 | 1261 |
| Day 1345- Post EOT Week 96 | 1345 | 1262 | |

* Day 30 will always be the day after Day 29, regardless of when Day 29 occurs.

Early termination (ET) visits for Cohort 1 participants will be assigned to analysis visits according to the following visit windows if participants do not enter the optional treatment period:

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Screening | -35 | | -1 |
| Day 1 | 1 | 1 | 1 |
| Day 2 | 2 | 2 | 2 |
| Day 3 | 3 | 3 | 9 |
| Day 15 | 15 | 10 | 22 |
| Day 29 | 29* | 23 | 43 |
| Day 57 | 57 | 44 | 71 |
| Day 85 | 85 | 72 | 99 |
| Day 113 | 113 | 100 | 127 |
| Day 141 | 141 | 128 | 155 |
| Day 169 | 169 | 156 | 211 |
| Day 253- Post EOT Week 12 | 253 | 212 | 295 |
| Day 337- Post EOT Week 24 | 337 | 296 | 379 |
| Day 421- Post EOT Week 36 | 421 | 380 | 463 |
| Day 505- Post EOT Week 48 | 505 | 464 | 589 |
| Day 673- Post EOT Week 72 | 673 | 590 | 757 |
| Day 841- Post EOT Week 96 | 841 | 758 | |

* Day 30 will always be the day after Day 29, regardless of when Day 29 occurs.

Early termination visits for Cohort 2 participants will be assigned to analysis visits according to the following visit windows if participants enter the optional treatment period:

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Screening | -35 | | -1 |
| Day 1 | 1 | 1 | 1 |
| Day 2 | 2 | 2 | 2 |
| Day 3 | 3 | 3 | 9 |
| Day 15 | 15 | 10 | 22 |
| Day 29 | 29 | 23 | 43 |
| Day 57 | 57 | 44 | 71 |
| Day 85 | 85 | 72 | 99 |
| Day 113 | 113 | 100 | 127 |
| Day 141 | 141 | 128 | 155 |
| Day 169 | 169 | 156 | 183 |
| Day 197 | 197 | 184 | 211 |
| Day 225 | 225 | 212 | 239 |
| Day 253 | 253 | 240 | 267 |
| Day 281 | 281 | 268 | 295 |
| Day 309 | 309 | 296 | 323 |

| | | | |
|---|---|---|---|
| Day 337 | 337 | 324 | 379 |
| Day 421 | 421 | 380 | 463 |
| Day 505 | 505 | 464 | 547 |
| Day 589 | 589 | 548 | 631 |
| Day 673 | 673 | 632 | 715 |
| Day 757- Post EOT Week 12 | 757 | 716 | 799 |
| Day 841- Post EOT Week 24 | 841 | 800 | 883 |
| Day 925- Post EOT Week 36 | 925 | 884 | 967 |
| Day 1009- Post EOT Week 48 | 1009 | 968 | 1093 |
| Day 1177- Post EOT Week 72 | 1177 | 1094 | 1261 |
| Day 1345- Post EOT Week 96 | 1345 | 1262 | |

Early termination visits for Cohort 2 participants will be assigned to analysis visits according to the following visit windows if participants do not enter the optional treatment period:

| **Analysis Visit** | **Target Analysis Day** | **Low Analysis Day** | **High Analysis Day** |
|---|---|---|---|
| Screening | -35 | | -1 |
| Day 1 | 1 | 1 | 1 |
| Day 2 | 2 | 2 | 2 |
| Day 3 | 3 | 3 | 9 |
| Day 15 | 15 | 10 | 22 |
| Day 29 | 29 | 23 | 43 |
| Day 57 | 57 | 44 | 71 |
| Day 85 | 85 | 72 | 99 |
| Day 113 | 113 | 100 | 127 |
| Day 141 | 141 | 128 | 155 |
| Day 169 | 169 | 156 | 183 |
| Day 197 | 197 | 184 | 211 |
| Day 225 | 225 | 212 | 239 |
| Day 253 | 253 | 240 | 267 |
| Day 281 | 281 | 268 | 295 |
| Day 309 | 309 | 296 | 323 |
| Day 337 | 337 | 324 | 379 |
| Day 421- Post EOT Week 12 | 421 | 380 | 463 |
| Day 505- Post EOT Week 24 | 505 | 464 | 547 |
| Day 589- Post EOT Week 36 | 589 | 548 | 631 |
| Day 673- Post EOT Week 48 | 673 | 632 | 757 |
| Day 841- Post EOT Week 72 | 841 | 758 | 925 |

| | | | |
|---|---|---|---|
| Day 1009- Post EOT Week 96 | 1009 | 926 | |

If the activity is not scheduled to occur at the assigned visit, then the closest scheduled visit for that activity will be assigned. If an ET visit is re-assigned to an analysis visit for which a scheduled visit occurred, then the data from the scheduled visit will be used in the analysis for that time point. For example, if the Dose #4/Day 85 visit occurred as scheduled and then a participant withdrew on Day 90 and came back in for ET assessments, the ET visit will be re-assigned to Day 85 based on the table above; however, the assessments from the scheduled Day 85 visit will be used for analysis of the Day 85 time point.

In addition, the measurements from all last visits will be summarized descriptively for all safety assessments.

### *3.1.3 Definitions of Baseline and End of Study*

Baseline (excluding the variable of serum AAT protein concentration) is defined as the last non-missing assessment prior to the first dose of study drug except for serum AAT where baseline is defined as the mean from all predose AAT measurements.

A participant is considered to have completed the study if he or she has completed all phases of the study (including F/U if applicable), including the last visit or the final scheduled procedure.

The end of the study is defined as the completion of the database lock.

### *3.1.4 Summary Statistics*

In general, summary statistics (number of non-missing values), mean, standard deviation, median, minimum and maximum, Q1, and Q3 values for continuous variables, and number and percentage of participants in each category for categorical variables) will be provided by treatment group and cohort for all variables. The denominator used for the percentage calculation will be clearly defined.

In summary tables and figures, data from scheduled visits, including F/U visits, will be included.

Listings will include all data from scheduled and unscheduled/ET visits.

### *3.1.5 Hypothesis Testing*

No hypothesis tests will be performed due to the early termination of the study. All data including demographic, PD and safety parameters will be summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, minimum, median, and maximum, Q1 and Q3 for continuous parameters; frequency and percentage for categorical parameters).

### *3.1.6 Handling of Dropouts and Missing Data Values*

As statistical analyses will be descriptive in nature, no missing data will be imputed unless otherwise specified. For the classification of treatment emergent adverse events (TEAE) and concomitant medications, the following imputation rules will be applied:

Dates will be printed in ISO 8601 date format (YYYY-MM-DD). If only year and month are available, date will be displayed as YYYY-MM. If only year, then just YYYY. Dates that are missing because they are not applicable for the subjects will be output as “NA”, unless otherwise specified.

Treatment emergent adverse events and concomitant medications with missing start dates will be considered as treatment-emergent unless the partial date excludes that possibility. Otherwise, the first day of the month will be used to impute the missing start day and January will be used to impute missing start month.

The purpose of imputing day and month values is to determine treatment emergence or whether a medication is a prior or a concomitant medication. The imputed value will not be presented in the listings. Only the derived TEAE status and concomitant medication status will be presented.

## 3.2 Analysis Populations

### *3.2.1 Enrolled Population*

The Enrolled Population is defined as all participants who sign the informed consent.

### *3.2.2 Safety Population*

The Safety Population is defined as all participants randomly assigned to study intervention and who received at least 1 dose of belcesiran/placebo. Participants will be analyzed according to initial dose received.

### *3.2.3 Pharmacokinetic (PK) Population*

The PK Population is defined as all participants randomly assigned to study intervention and who received at least 1 dose of belcesiran and have at least 1 postdose PK assessment.

### *3.2.4 Pharmacodynamic (PD) Population*

The PD Population is defined as all participants randomized who received at least 1 dose of belcesiran/placebo and have at least 1 postdose PD assessment.

### *3.2.5 Evaluable Population*

The Evaluable Population is defined as all participants randomly assigned to study intervention and who received at least 50% of planned doses of belcesiran/placebo.

The PK and evaluable population will not be considered for the analysis due to the early termination of the study.

## 3.3 Subject Data and Study Conduct

### *3.3.1 Participant Disposition*

Counts and percentages of participants who completed the treatment period, who completed the treatment period but did not complete the follow-up, who completed the study, and who discontinued from the study will be summarized based on the Enrolled Population. Reasons for early discontinuation will also be summarized.

### *3.3.2 Demographic and Baseline Characteristics*

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) ($kg/m^2$)
- F1, F2, F3 and F4

- AST
- ALT
- Serum AAT
- Receiving augmentation therapy

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of participants as appropriate by treatment and overall, based on the Safety Population.

## 3.4 Safety & Efficacy Assessment

### *3.4.1 Primary Endpoint for Cohorts 1 and 2*

Safety Analysis:

All safety analyses will be performed on the Safety Population. The details of the safety analysis are described in section 3.7.

Serum AAT Concentrations Analysis:

Serum AAT protein concentration observed data, absolute change from baseline, and percent change from baseline will be summarized with descriptive statistics by treatment and time point, based on the PD Population.

The data from the date of and onwards of augmentation therapy received will be excluded from the analysis. The augmentation therapy includes Prolastin® and Glassia®.

Correspondingly, figures for observed serum AAT protein concentration longitudinal trajectory, absolute change from baseline, and percent change from baseline will be presented by line plot (mean ± standard error (SE)) at the individual level and at the cohort level using the linear scale. Figures will include all study periods, relevant references and legends.

The serum AAT concentration will be analyzed by using a linear log-normal regression model by combining Cohort 1 and Cohort 2 together. The linear log-normal regression will include treatment, baseline value and randomized stratification factor for fibrosis types (F1/F2, F3 and F4) as covariate and the change from baseline in serum AAT as the response variable.

The sample SAS code is as follows.

```
/************************************
datain=Input data set
TRT= Treatment (0-Placebo, 1-Belcesiran 210 mg)
FIB= Fibrosis types (F1/F2, F3, and F4)
BASE=Baseline serum
CHG= Serum change in Week 24 from baseline
************************************/
proc genmod data=datain;
class TRT FIB;
model CHG = TRT BASE FIB / dist=normal link=log;
lsmeans TRT/ PDiff CL alpha=0.05;

run;
```

The least square mean difference between the Belcesiran 210 mg and Placebo, standard error, and the confidence interval will be reported.

The P-value will not be reported since the hypothesis test will not be performed.

### *3.4.2 Primary Endpoint for Cohort 3*

There are no data for Cohort 3 due to the early termination of the study prior to enrolling participants in this cohort. Therefore, no analysis is planned for Cohort 3.

### *3.4.3 Secondary Endpoints*

Analyses of Fibrosis, Steatosis, and Inflammation

Descriptive summaries will be provided for METAVIR scores, and Ishak scores. METAVIR scores are composed of a 2-letter and 2-number coding system that describes activity (A) and fibrosis (F). Ishak scores range from 0 (no fibrosis) to 6 (cirrhosis) and will be analyzed as a continuous variable.

Values and changes from baseline (if applicable) will be presented at each scheduled visit by treatment and overall. Listings of the individual parameters will be provided.

## 3.5 Pharmacokinetic (PK) Assessment

There is no PK analysis planned for the study.

## 3.6 Pharmacodynamic (PD) Assessment

There is no PD analysis planned for the study.

## 3.7 Safety Assessment

Safety and tolerability of study drug will be evaluated via the assessment of AEs, the change from Baseline in PFTs, 12-lead ECG, PE findings, vital signs, and clinical laboratory tests. All safety analyses will be performed on the Safety Population (unless specified otherwise) by actual treatment received and overall.

### *3.7.1 Adverse Events (AEs)*

AEs will be captured from the date of informed consent through study completion. AEs will be defined as TEAEs if they have a start date on or after the administration of study drug during the treatment period, or if they occur prior to the administration of study drug and worsen in severity/grade or relationship to the investigation medical product after the administration of study intervention during the treatment period. Frequency and percentages will be used to summarize TEAEs, serious adverse events (SAEs), AEs of special interest (defined as injection site reactions), and TEAEs by relationship.

An overview of TEAEs will be provided including counts and percentages of participants with the following:

- Any TEAEs (overall and by maximum severity)
- Any TEAEs (overall and by relationship to study medication)
- Any TEAEs of special interest (overall and by injection site reaction grading)
- Any SAEs
- Any TEAEs leading to discontinuation of study drug
- Any AEs leading to death

Counts and percentages of participants will also be presented by system organ class and preferred term for each of the categories in the overview. Participants will be counted only once at each system organ class and preferred term level.

Listings will be presented specifically for TEAEs, SAEs, and TEAEs leading to discontinuation of study drug.

### *3.7.2 Pulmonary Function Tests (PFTs)*

PFTs include the following parameters: forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC), $FEV_1$/FVC, and diffusing capacity of the lungs for carbon monoxide (DLCO).

Values, absolute changes from baseline, and percent change from baseline will be presented at each scheduled visit by treatment and overall. Any value of $FEV_1$/FVC larger than 1 will be excluded from the summary table but included in the listing.

The DLCO ($mL.min^{-1}.mmHg^{-1}$) will be evaluated as below:

$$DLCO_{Male} = \exp(-7.664278 + 2.151173\ \ln(height) - 0.027927\ln(age) + Mspline)$$

$$DLCO_{Female} = \exp(-7.914474 + 2.171106\ \ln(height) - 0.025634\ \ln(age) + Mspline)$$

The height and age are expressed as centimeters and years, respectively. The Mspline values are collected from the supplementary documents of article Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians.

### *3.7.3 Clinical Laboratory Tests*

Results of clinical laboratory tests will be descriptively summarized as follows: For continuous laboratory parameters, actual values at each scheduled visit (including follow-up visits) and absolute changes from baseline will be summarized. For categorical laboratory parameters, numbers and percentages of participants in each test result category will be presented by visit.

By-participant listings will be presented by clinical laboratory test parameters, values outside the reference ranges will be flagged.

### *3.7.4 Vital Signs*

Vital sign parameters include height, weight, oral temperature, heart rate, respiratory rate, and blood pressure (systolic and diastolic). The observed values at each visit, baseline and absolute change from baseline to post-baseline visits values will be summarized using descriptive statistics. By-participant listing of vital sign parameters will be provided.

### *3.7.5 Electrocardiograms*

Standard 12-lead ECGs will be performed in the supine position after the participant has rested comfortably for 10 minutes. 12-Lead ECGs will be obtained using a machine that automatically calculates the heart rate and ventricular rate and measures RR, PR, QRS, QT, and corrected QT intervals (QTcF, Fridericia correction). For each 12-lead ECG parameter, observed values at each visit, baseline and absolute change from baseline to post-baseline visit values will be summarized using descriptive statistics.

A summary of QTc and QTcF measurements will be performed, within treatment group and time point, using counts and percentages of the number of participants with assessments that meet the following criteria: absolute QTc or QTcF > 500 msec, QTc or QTcF with a change from baseline >60 msec.

For the overall interpretation of the ECG profile, the number and percentage of participants in each category (Normal, Abnormal Not Clinically Significant, or Abnormal Clinically Significant) recorded on the CRF will be presented by visit and by treatment and overall. 12-Lead ECG data will be listed by participants.

### *3.7.6 Physical Examinations (PE)*

For the overall interpretation of the PE, the number and percentage of participants in each category (Normal, Abnormal Not Clinically Significant, or Abnormal Clinically Significant) recorded on the CRF will be presented by visit and by treatment and overall. Physical examination data will be listed by participant.

### *3.7.7 Other Safety Assessments*

Total complement hemolytic activity (CH50, including C3a, C5a, and Bb), serum alpha fetoprotein (AFP), coagulation parameters (aPTT, PT, and INR), antidrug antibodies, and C-reactive protein will be summarized using descriptive statistics for each visit by treatment and overall. Listings will also be provided.

# 4 DATA SAFETY MONITORING COMMITTEE

A Data Safety Monitoring Committee (DSMC) will monitor the safety of participants over the course of the study. Table 7 of the protocol shows the minimal required timing of reviews by the DSMC. Ongoing risk-benefit assessments will be conducted throughout the trial by the independent DSMC. In addition, DSMC will provide a comprehensive review of study safety, tolerability, and PK/PD data, along with a summary of cohort reviews across all cohorts and provide decisions. Further operational details will be pre-specified in the DSMC charter.

# 5 ANALYSIS TIMING

## 5.1 Interim Analysis

There are no interim analyses planned due to the early termination of the study.

## 5.2 Final Analysis

The study was terminated prior to enrolling the participants into Cohort 3. The database will be locked after completion of the follow-up for Cohort 1 and Cohort 2 participants. The study will be unblinded at the participant level and the final analysis will be generated. The final analysis will be performed on all available data as described in the above sections of SAP. The corresponding tables, figures, and listings (TFL) will be provided after the database lock.

In addition to TFLs, Study Data Tabulation Model (SDTM) data and ADaM data along with associated files will be provided. Associated files may include the following: annotated CRFs, SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, and TFL programs.

# 6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

This SAP does not deviate from the statistical analysis described in v3.0 of the protocol. Any deviations from the protocol or SAP will be described in the CSR.

# 7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in participant data listings which will be sorted by participant and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.