Statistical Analysis Plan: DS102A-02

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Signature

I have carefully read this statistical analysis plan and agree to the described methods and proceedings.

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LIST OF ABBREVIATIONS

15(S)-HEPE EE	15(S)-Hydroxy-Eicosapentaenoic Acid Ethyl Ester
Adipo-IR	Adipose Tissue Insulin Resistance
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic-Chemical
BMI	Body Mass Index
CAP	Controlled Attenuation Parameter
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DOA	Drugs of Abuse
ECG	Electrocardiogram
ELF	Enhanced Liver Fibrosis score
HOMA-IR	Homeostatic model assessment Insulin Resistance
LS Mean	Least Square Mean
MAR	Missing at Random
MedDRA™	medical dictionary for regulatory activities
MMRM	Mixed Model of Repeated Measurements
NAFLD	Non-Alcoholic Fatty Liver Disease
NFS	NAFLD Fibrosis Score
PT	Preferred Term
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAEs	Treatment-Emergent Adverse Events
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) for study DS102A-02 describes the detailed procedures for executing the planned statistical analyses for this study.

This version of SAP has been written to be in accordance with the Protocol dated August 24, 2018 and the Case Report Form (CRF) dated November 28th, 2016. Any further changes to the protocol or CRF may necessitate updates to the SAP. This SAP was written as a separate document, completed after finalizing the protocol, and prior to locking and unblinding the clinical datasets. This SAP includes a more technical and detailed elaboration of the statistical analyses stated in the protocol.

The statistical analyses will be conducted by Brightech International using the SAS® software version 9.2 or later.

2. STUDY OBJECTIVES

The objective of the study is to assess the safety and efficacy of orally administered DS102 capsules versus placebo in the treatment of adult patients with Non-Alcoholic Fatty Liver Disease (NAFLD).

3. STUDY DESIGN

This study will involve two dose levels of DS102 1000mg per day (500mg BD), 2000mg per day (1000mg BD) or placebo BD for 16 weeks using three treatment groups consisting of 32 patients each.

Patients with diagnosed NAFLD (Non-Alcoholic Fatty Liver Disease) will be enrolled in the study. After assessment and documentation of the baseline disease characteristics by the investigator, the patient will be randomly assigned to one of the above-mentioned treatment groups. The patient will be provided with study medication containing one of the assigned doses of DS102 or placebo according to the randomization. During the 16 weeks of treatment patients will take one of the treatments twice daily with or after food (morning and evening).

Evaluation of efficacy will be performed throughout the study. A follow-up visit will be performed 4 weeks after the last date of treatment to monitor the treatment effects in comparison to the end of treatment.

4. STUDY POPULATIONS

4.1. Enrolled Set

The **Enrolled Set** includes all patients who signed the informed consent form.
Screen failures are patients from the Enrolled Population who do not meet the eligibility requirements and are withdrawn from the study prior to randomization.

4.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized patients who received at least one administration of study treatment and have at least one post-baseline measurement. Patients will be analyzed according to the treatment they were assigned to at randomization, irrespective of what treatment they actually received.

4.3. Safety Analysis Set

The Safety Analysis Set (SAF) consists of all patients who take at least one administration of study treatment. Patients will be analyzed according to the treatment actually taken.

4.4. Per Protocol Set

The Per-Protocol Set (PPS) will be a subset of the Full Analysis Set consisting of those patients in the FAS who had no major protocol violations.

5. STUDY ENDPOINTS

5.1. Primary Endpoints

Primary Efficacy Endpoint

- Change in serum ALT (alanine aminotransferase) from baseline to week 16.
- Change in liver stiffness measurements by Transient Elastography from baseline to week 16

Primary Safety Endpoint

Percent of subjects with treatment emergent adverse events (TEAEs) in each treatment group leading to treatment discontinuation.

5.2. Secondary Endpoints

- Change in serum ALT (alanine aminotransferase) from baseline to weeks 2, 4, 8 and 12.
- Change in serum AST (aspartate aminotransferase) from baseline to weeks 2, 4, 8, 12 and 16.
- Change in AST: ALT ratio from baseline to weeks 2, 4, 8, 12 and 16.
- Change in FIB-4 Index from baseline to week 16.
- Change in NAFLD fibrosis score (NFS) from baseline to week 16.
- Change in hepatic fat measured by CAP (controlled attenuation parameter) from baseline to week 16.
- Change in ELF (Enhanced Liver Fibrosis score) from baseline to week 16.
- Change in HOMA-IR/Adipo-IR (Homeostatic model assessment Insulin Resistance / Adipose tissue Insulin Resistance) from baseline to weeks 2, 4, 8, 12 and 16.

6. STATISTICAL CONSIDERATIONS

6.1. Estimation of Sample Size

Assuming a 20% delta in the percentage response between active drug and placebo arms, a standard deviation of 25% and a dropout rate of 20%, this results in 32 patients per group with 5% level of significance, and 80% power.

The sample size may be re-estimated at an interim analysis based on recommendation from an unblinded, independent DSMB. The sample size may be increased up to a maximum of 150 patients in total to achieve a conditional power of 80% for the primary endpoint.

6.2. General Considerations

Summary statistics for continuous variables will include mean, standard deviation, median and range. Categorical variables will be presented as frequency counts and percentages. Data listings will be created to support tables and present data.

All statistical analyses will be conducted using SAS® Version 9.2 or above (SAS Institute, Cary, NC). Graphical summaries will be produced using SAS®. All probability values under the null hypotheses shown in the tables will be rounded to 3 decimal places. If a rounded p-value is equal to 0.000, the result will be displayed as "<0.001" in the tables. For presentation of untransformed data, the mean and median will be presented to one decimal place greater than the original data, standard deviation will be to two decimal places greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data.

6.3. Analysis Definitions

6.3.1. Naming Conventions for Study Day

For the purpose of statistical computation, the study day of all assessments that are performed on or after randomization will be calculated as:

Study Day = date of the assessment – date of randomization + 1.

For assessment performed before the date of randomization, the study day calculation is similar except without adding 1:

Study Day= date of assessment – date of randomization.

6.3.2. Baseline Values and Changes from Baseline

The baseline value of all efficacy and safety variables is defined as the last non-missing data on or prior to randomization.

Change from baseline is defined as post-baseline value – baseline.

7. DATA ANALYSIS

7.1. Patient Disposition

Patient disposition data will be summarized for all screened patients as well as for all randomized patients presented (for all analysis populations) by treatment group. The number of subjects who were screened will be presented; number of patients who failed screening, who were enrolled, who were randomized will also be presented, along with the percentages based on number of screened subjects. Percentage will also be calculated for randomized subjects based on number of patients enrolled.

The following patient disposition data will be summarized with percentages based on the number of patients randomized:

- The number and percentage of patients who completed the study.
- The number and percentage of patients who were enrolled but discontinued, along with the reason for discontinuation (e.g., lost to follow-up, adverse event, death, withdraw by patients).

7.2. Treatment Compliance

Treatment compliance is defined as the number of capsules taken over the number of capsules that should have been taken:

%Compliance = (number of capsules actually taken / 448) * 100%

448 (the number of capsules supposed to be taken) = 2 * 2 capsules /day * 7 days/week * 16 weeks

For patients with premature termination, the number of capsules supposed to be taken will be adjusted for the actual duration of study participation.

Drug exposure days is defined as the number of days from first treatment to last treatment including days in between when study drugs were not taken. Descriptive statistics of subjects' drug exposure days, number of capsules taken, and treatment compliance will be tabulated by treatment group. Individual's treatment compliance will be listed.

7.3. Protocol Deviations

Protocol deviations will be reviewed to determine if it is a major deviation, which would render the violators excluded from the per-protocol population.

Number and percentage of subjects in each treatment group with major protocol deviations will be presented. Individual protocol deviations will be listed with detailed deviation term.

7.4. Demographic and Baseline Characteristics

Statistical summaries and analysis of the demographic and baseline data will be based on the Safety and Full Analysis sets. Tables will be presented by treatment group. These variables may include the following:

- Gender
- Race
- Ethnicity
- Age (years)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

For continuous variables (e.g., age, weight, etc.), descriptive summary statistics will include the number, mean, standard deviation, median, minimum and maximum values. For categorical variables (e.g., sex, race, etc.), descriptive summary statistics will include the frequency distribution (i.e., number and percentage) among the categories.

Medical history data will be listed including information of start date, end date, severity, and treatment for the event or not.

Prior and concomitant Medications verbatim terms will be encoded using WHO Drug Dictionary (WHODD) codes and presented by Anatomical Therapeutic-Chemical (ATC) classifications in alphabetical order by treatment group.

7.5. Efficacy Evaluation

7.5.1. General Considerations

The primary efficacy variables (serum ALT and liver stiffness) will be the change from baseline to week 16 (Visit 10). For each primary efficacy variable, the two active treatment groups will be compared against placebo via an analysis of covariance (ANCOVA) model, including the corresponding baseline value as covariate. The comparisons against placebo will be done according to Dunnett's multiple testing procedure (for multiple dose vs. placebo comparison). The two primary endpoints will be assessed independently in efficacy analyses. Efficacy analysis will be performed on the Full analysis set and per-protocol set.

7.5.2. Efficacy Analyses on ALT, AST, AST:ALT and HOMA-IR, Adipo-IR

ALT, AST, AST:ALT and HOMA-IR, Adipo-IR are all assessed at Baseline visit, visit 3/week 2, visit 4/week 4, visit 6/week 8, visit 8/week 12 and visit 10/week 16. ALT, AST, AST:ALT and HOMA-IR, Adipo-IR will be analyzed separately.

The change from baseline to weeks 2, 4, 8, 12 and 16 of these efficacy variables will be calculated by the post-baseline assessment at respective time point minus the baseline assessment result. Descriptive statistics of actual values of ALT, AST, AST:ATL or HOMA-IR, Adipo-IR and change from baseline to weeks 2, 4, 8, 12 and 16 will be presented by treatment group. At each time point, the change from

baseline will be analyzed using an analysis of covariance (ANCOVA) model with terms of treatment, site, baseline and treatment-by-baseline interaction. The pairwise comparisons among the treatment groups will also be presented. Dunnett's t-test will be used for the comparison between the two doses of DS102 and placebo.

As an overall treatment effect analysis, the change from baseline of these variables over weeks 2, 4, 8, 12 and 16 will be analyzed using a mixed model of repeated measurements (MMRM) under assumption of missing at random (MAR). The model will include treatment group, visit (week 2, 4, 8, 12 and 16), treatment-by-visit interaction as fixed effects, and corresponding baseline as well as treatment-by-baseline interaction terms. The model will be run using unstructured covariance assumptions. Degrees of freedom will be adjusted using the Kenward-Roger method.

From this repeated measurement analysis, the least squares (LS) means and corresponding 95% confidence intervals (CI) for each treatment group, along with overall and pair-wise p-values will be presented. If only one null hypothesis for one primary endpoint is rejected, then the confidence intervals for the endpoint will be adjusted according to the Dunnett's test.

The LS means of these endpoints along with the 95% CI for each treatment group will be displayed as a figure over time.

7.5.3. Efficacy Analyses on Liver stiffness, FIB-4, NFS, Hepatic fat and ELF

Liver stiffness, FIB-4, NFS, Hepatic fat and ELF are all assessed at Baseline visit and visit 10/week 16. FIB-4, NFS, Hepatic fat, Liver stiffness and ELF will be analyzed separately.

The change from baseline to week 16 of these efficacy variables is defined as the assessment result at week 16 minus baseline assessment result. Descriptive statistics of actual value of Liver stiffness, FIB-4, NFS, Hepatic fat, or ELF and change from baseline to week 16 will be presented by treatment group.

The analyses of change from baseline to week 16 of these efficacy variables will use the Full Analysis Set data. To compare the group means, an analysis of covariance (ANCOVA) model will be used with baseline, treatment, treatment-by-baseline and site effects. The pairwise comparisons of treatment groups will be presented.

This ANCOVA analysis will apply to both primary endpoints.

Same ANCOVA model will be performed on per protocol set as supportive analyses.

7.5.4. Missing values

For missing data in efficacy endpoint, the last observation carried forward (LOCF) analysis will be performed. Further, a controlled multiple imputation approach based on pattern mixture models will be applied. More specifically, missing data for those subjects taking DS102 who discontinued will be imputed based on the posterior

distribution of the placebo group. All other missing data will be assumed under a MAR and imputed using the posterior distribution of the respective treatment group.

7.6. Safety Evaluation

The safety analyses will use the safety population.

7.6.1. Adverse Events

Adverse events (AEs) will be coded by Medical Dictionary for Regulatory Activities (MedDRA™) System Organ Class (SOC) and Preferred Term (PT). Causality (relationship to study drug) of AEs will be summarized. If more than one adverse events are recorded for a patient within any SOC or PT term, the patient will only be counted once on the most severe grade and the closest relationship to treatment.

Treatment-emergent adverse events (TEAEs) will be defined as the adverse events with date of onset (or worsening) on or after the date of first treatment.

The following AE summaries will be presented in tables:

- An overall summary of the AEs, including the number of AE reported, number of TEAE reported, number and percentage of patients reporting AE, the number and percentage of patients with AE possibly related or related to study treatment, number and percentage of patients reporting serious AE, the number and percentage of patients with serious AE possibly related or related to study treatment, the number and percentage of patients discontinuing treatment due to AE, the number and percentage of patients' death due to AE, presented by treatment group.
- A breakdown of the number and percentage of patients reporting TEAEs, categorized by SOC and PT, presented by treatment group.
- A breakdown of the number and percentage of patients reporting TEAEs, categorized by SOC and PT, presented by treatment group and severity.
- Number and percentage of patients reporting TEAEs, leading to treatment discontinuation, categorized by SOC and PT, presented by treatment group. Patients' TEAEs leading to treatment discontinuation will also be listed.
- Patients with TEAEs possibly related or related to study treatment, categorized by SOC and PT, presented by treatment group.
- Patients with TEAEs possibly related or related to study treatment, categorized by SOC and PT, presented by treatment group and severity.
- Number and percentage of patients reporting Serious AEs (SAEs), categorized by SOC and PT, presented by treatment group.
- Number and percentage of patients reporting Serious AEs (SAEs), categorized by SOC and PT, presented by treatment group and severity.

7.6.2. Laboratory Data

Laboratory data will be presented in following ways:

- Descriptive statistics will be tabulated for biochemistry, hematology, continuous urinalysis parameters, lipid profile and coagulation parameters by treatment group and visit. Number and percentages will be tabulated for qualitative urinalysis

parameters. Laboratory parameters will be grouped by panel (biochemistry, hematology, urinalysis, lipid profile and coagulation tests) and sorted alphabetically.

- Shift tables comparing the baseline parameter classification (low, normal, high) to each post-baseline visit classification for all non-missing post-baseline data will be provided for biochemistry, hematology, urinalysis, lipid profile and coagulation tests data, by treatment group.
- Abnormal clinically significant lab values will be tabulated by treatment group and visit.
- Clinical laboratory values will be listed for each patient by treatment and study visit.

7.6.3. Vital Signs

Descriptive statistics of patients' vital signs by treatment group and scheduled study visit will be summarized including number of patients, mean, standard deviation, median and range.

Individual values of vital signs will be listed.

The following equation will be used to calculate Body Mass Index (BMI):

$BMI = \text{Weight (kg)} / (\text{Height (m)})^2$

7.6.4. Physical Examination

Exam results of physical examinations are recorded as "Normal", "Abnormal, not clinically significant" or "Abnormal, clinically significant". Number and percentage of subjects in each category will be summarized.

7.6.5. Alcohol urine test and Drug of Abuse (DOA) test

Findings of alcohol urine test and DOA test will be listed for each patient.

7.6.6. ECG Assessment

Number and percentage of subjects in each ECG evaluation result category (normal, abnormal not clinical significant, abnormal clinical significant) will be summarized by treatment group and study visit.

Evaluation of 12-lead ECG assessment results will be presented by treatment group and study visit.

12-lead ECG assessment will be listed for each patient with all associated comments and summarized by treatment group and study visit.

7.6.7. Virology Analysis

Number and percentage of subjects in each category of virology analyses results will be summarized

7.7. Pharmacokinetic Analysis

Plasma pharmacokinetic samples are planned to be collected pre-dose at Baseline Visit (Visit 2), Week 2 (Visit 3), Week 4 (Visit 4), Week 8 (Visit 6), Week 12 (Visit 8), Week 16 (Visit 10) and Week 20 (Visit 11). Elapsed Time will be calculated as time difference between Time of Pharmacokinetic Sample Collection and Time of Study Drug Administration and listed for each subject. Descriptive statistics (mean, standard deviation, median, minimum and maximum) of plasma concentrations of 15(S)-HEPE (15(S)-Hydroxy-Eicosapentaenoic Acid Ethyl Ester) will be summarized by treatment group and visit. Mean plasma concentration-time profiles of 15(S)-HEPE will be presented by treatment group graphically.

7.8. Exploratory Assessment

Blood samples will be collected and stored for potential gene array analysis and biomarker analysis. Individual data will be listed for each patient by treatment group and study visit.

8. INTERIM ANALYSES

The sample size may be re-estimated at an interim analysis based on recommendation from an unblinded, independent DSMB. The sample size may be increased up to a maximum of 150 patients in total to achieve a conditional power of 80% for either of the primary endpoints or the secondary endpoints.

- Futility will be declared if the conditional power is <=50% for both primary endpoints and all secondary endpoints and for both active groups compared to Placebo; this is equivalent to say that none of the four primary comparisons and the supportive secondary comparisons to Placebo shows an advantage of Active over Placebo.
- High efficacy will be declared if the smallest p value of the 4 primary comparisons versus Placebo (adjusted by the Dunnett procedure) is smaller than $p<0.01$

9. PLANNED SUMMARY TABLES AND LISTINGS

Planned table numbering and title may be modified for the clinical study report (CSR), with the final list to be reflected in a separate table, figure and listing shell document.

10. REFERENCE

Clinical Trial Protocol: A Randomized, Double-Blind, Placebo-Controlled, Exploratory Phase IIa Study to Assess the Safety and Efficacy of Orally Administered DS102 in NAFLD Patients, DS102A-02 Version 6.0 August 2018, Afimmune,