# A Randomised, Double-Blind, Placebo-Controlled, Phase II Study to Assess the Efficacy and Safety of Orally Administered DS102 in Patients with Severe Acute Decompensated Alcoholic Hepatitis

## Afimmune Study No: DS102A-05-AH1
## Syne qua non Ltd Study No: ANE18001

# Statistical Analysis Plan

**Version: Final 1.0**

**Date: 25th January 2019**

### For Syne qua non Ltd – Lead Statistician

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AH | Alcoholic Hepatitis |
| AIC | Akaike's Information Criterion |
| ALT | Alanine Transaminase |
| APACHE II | Acute Physiologic and Chronic Health Evaluation II |
| AST | Aspartate Transaminase |
| $AUC_{inf}$ | Area under the concentration-time curve extrapolated to infinite time |
| $AUC_t$ | Area under the concentration-time curve to time t |
| $AUC_{tau}$ | Area under the concentration-time curve to the end of the dosage interval |
| BD | Twice a day |
| BDRM | Blinded Data Review Meeting |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| $C_{max}$ | Maximum Observed Concentration |
| CNS | Central Nervous System |
| CI | Confidence Interval |
| CS | Clinically Significant |
| DSMB | Data and Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| FAS | Full Analysis Set |
| Flucp | Fluctuation at pharmacokinetic steady-state |
| GT | Gamma Glutamyl Transferase |
| HIV | Human Immunodeficiency Virus |
| IMP | Investigational Medicinal Product |
| INR | International normalised ratio |
| Kel | Apparent first-order terminal elimination rate constant |
| $\lambda_z$ | Terminal Elimination Rate Constant |
| LLOQ | Lower Limit of Quantification |
| LS | Least Squares |
| MAR | Missing at Random |
| MDF | Maddrey Discriminant Function |
| MedDRA | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| MELD | Model End-stage Liver Disease |
| MMRM | Mixed-Model Repeated Measures |
| m-SOFA | Modified Sequential Organ Failure Assessment |
| NASH | Non-Alcoholic Steatohepatitis |
| NCS | Not Clinically Significant |
| %Extrap | Percentage of AUCinf obtained by extrapolation |
| PK | Pharmacokinetic |
| PKAP | Pharmacokinetic data analysis plan |
| PPS | Per Protocol Set |
| PT | Preferred Term |
| Q1 | $25^{th}$ percentile |
| Q3 | $75^{th}$ percentile |
| $R_{ac}$ | Accumulation ratio at pharmacokinetic steady-state |
| RAN | All Randomised Patients |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| $t_{1/2}$ | Terminal Elimination Half-Life |
| TEAE | Treatment Emergent Adverse Event |
| $t_{max}$ | Time of the Maximum Observed Plasma Concentration |
| $T_{ss}$ | Time to achieve pharmacokinetic steady-state |
| WHO Drug | World Health Organization Drug Dictionary |

# 1 INTRODUCTION

This document details the statistical analysis of the data that will be performed for the Afimmune study: A Randomised, Double-Blind, Placebo-Controlled, Phase II Study to Assess the Efficacy and Safety of Orally Administered DS102 in Patients with Severe Acute Decompensated Alcoholic Hepatitis.

The proposed analysis is based on the contents of Version 4.0 of the protocol (dated 01-AUG-2018). In the event of future amendments to the protocol, this statistical analysis plan (SAP) may be modified to account for changes relevant to the statistical analysis.

The table, listing and figure shells are supplied in a separate document.

# 2 STUDY OBJECTIVES AND DESIGN

## 2.1 Study Objectives

*Efficacy Objective:*

• To compare the efficacy of orally administered DS102 versus placebo, in the treatment of adult patients with severe acute decompensated Alcoholic Hepatitis (AH).

*Safety Objective:*

• To compare the safety of orally administered DS102 versus placebo, in the treatment of adult patients with severe acute decompensated AH.

*Pharmacokinetic Objective:*

• To evaluate the pharmacokinetics (PK) of 15(S)-HEPE following orally administered DS102 capsules, in six adult patients with AH in an initial pilot phase of the study, followed by trough level assessment of 15(S)-HEPE in all study participants.

## 2.2 Study Endpoints

The primary endpoint of the study is:

- Percentage change in Model End-stage Liver Disease (MELD) score from baseline to Day 28.

The secondary endpoints are:

- Change in total bilirubin from baseline to Day 7, 14, 21 and 28
- Proportion of patients showing a 25% reduction of bilirubin at day 7, 14, 21, and 28
- Change in serum Cytokeratin 18-M30/M65 from baseline to Day 7, 14, 21 and 28
- Change in Aspartate Transaminase (AST) levels from Baseline to Day 7, 14, 21 and 28
- Change in AST: Alanine Transaminase (ALT) ratio from Baseline to Day 7, 14, 21, 28
- Change in Maddrey Discriminant Function (MDF) score from baseline to Day 7, 14, 21 and 28

- Proportion of patients showing a 25% reduction in MELD score from baseline to Day 7, 14 and 21
- Change in MELD score from baseline to Day 7, 14 and 21
- Change in modified sequential organ failure assessment (m-SOFA) from baseline to Day 7, 14, 21 and 28
- Proportion of patients with a 2-point worsening of m-SOFA from baseline at Day 7, 14, 21 and 28
- Change in hepatic encephalopathy as assessed by West Haven criteria, from baseline at Day 7, 14, 21 and 28
- Incidence of acute kidney injury over 28 days (defined by requiring medicinal or mechanical support)
- Incidence of variceal haemorrhage, ascites or hepatic encephalopathy over 28 days

The exploratory endpoints are:

- Survival at day 7, 14, 21, 28 and 90 using Kaplan-Meier Plot
- Change in Gamma Glutamyl Transferase (GT) from baseline to Day 7, 14, 21 and 28
- Change in ALT from baseline to Day 7, 14, 21 and 28.
- Change in Child-Pugh score from baseline to Day 7, 14, 21 and 28
- Change in Acute Physiologic and Chronic Health Evaluation (APACHE) II score from baseline to Day 7, 14, 21 and 28
- Change in Lille score from baseline to Day 7, 14, 21 and 28

The safety endpoints are:

- Treatment emergent serious adverse events (SAEs), adverse events (AEs) and suspected unexpected serious adverse reactions (SUSARs)

## 2.3 Study Design

This is a randomised, placebo-controlled, double-blind, parallel group, multicentre, exploratory phase II study preceded by an open label pilot phase to investigate the efficacy and safety of orally administered DS102 capsules in patients with acute decompensated AH aged over 18 years. Patients will be recruited from 50 sites across 9 countries.

The open label pilot phase is a single arm study, all 6 patients will receive study drug (2 x DS102 500mg capsules orally administered twice a day (BD) (four capsules daily)), for 28 days. Results of the pilot phase will be assessed by a data and safety monitoring board (DSMB) for safety and if dose adjustments for the main study are needed.

After the open-label pilot phase of the study, two parallel groups of patients will be enrolled into the randomised double-blind phase of the study to compare one dose of DS102 with placebo over a 28-day treatment period. Patients will receive standard of care therapy in addition to their assigned investigational medicinal product (IMP)

throughout the treatment period of the study. It is planned that 120 evaluable patients, 60 per treatment group, will be randomised.

The study population will consist of male and female patients diagnosed with severe acute decompensated AH aged 18 years and over.

## 2.4 Visit Structure

During the study, 8 visits to the clinic are scheduled after the screening visit (Visit 1): one at the start of the comparative treatment period (Baseline/Visit 2) and six in the comparative treatment period (Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28 or Early Termination).

A final safety follow-up visit (Visit 9/Day 90) will be conducted on Day 90.

Both the pilot and main, double-blind, phase will follow the same structure.

Full details of the visit structure and scheduled assessments are detailed in the study protocol section 8 Study Conduct and Appendices 1 and 2.

# 3 SAMPLE SIZE

To discover an effect size of 0.54 (=Difference in means/standard deviation) in MELD change from baseline with 80% power, 55 patients per group are necessary under ideal assumptions using the t-test for independent samples (alpha=0.05, two-sided).

To take deviations from ideal parametric conditions and drop-outs into account, 60 patients per group will be randomised.

# 4 RANDOMISATION

For the main, double-blind phase, approximately 120 patients will be randomised into double blind treatment groups in a 1:1 ratio as follows:

- Treatment group A: 2 x placebo 500mg capsules orally administered BD (four capsules daily) for 28 days

- Treatment group B: 2 x DS102 500mg capsules orally administered BD (four capsules daily) for 28 days

# 5 INTERIM ANALYSIS

An interim analysis may be conducted in the main, double-blind phase once 50% of planned patients have completed their Day 28 assessments. Details of this will be covered in a detailed Interim Analysis Plan in accordance with Sponsor standard operating procedure (SOP) “Interim Analysis of Clinical Studies” and is not covered by this SAP.

# 6 ANALYSIS PLAN

## 6.1 General

The decision to proceed to the double-blind phase of this study will be determined by the DSMB following review of the safety and pharmacokinetic data from the pilot phase as detailed in the DSMB charter. No statistical outputs will be produced for the DSMB review as part of this SAP, details of the PK analysis for the pilot study are included in Appendix 1. Patients from the pilot phase will be included in the same listings for the double-blind phase as a separate group. Should the study be discontinued after the pilot phase, the listings described in the sections below will be produced for the pilot phase only.

The summary tables and figures described in the following sections relate to the main, double-blind, study only unless specifically mentioned otherwise.

Summary statistics for continuous variables will consist of number of non-missing observations (n), mean, standard deviation (SD), minimum, 25$^{th}$ percentile (Q1), median, 75$^{th}$ percentile (Q3), and maximum, unless specified otherwise. The precision of these variables is defined in the table, figure and listing shells document.

For categorical variables the number and percentage of patients in each category will be presented, based on the number of non-missing observations apart from disposition of patients, protocol deviations, background and demographic characteristics, prior and concomitant medications/procedures and adverse events where the percentage will be based on the number of patients in the analysis set.

All statistical tests will be performed using a two-tailed 5% overall significance level, unless otherwise stated. The null hypothesis at all times will be that the treatments are equivalent. All comparisons between the treatments will be reported with 95% confidence intervals for the difference.

## 6.2 Blinded Data Review Meeting

The Sponsor will convene a blinded data review meeting (BDRM) after the data has been cleaned and before the study is unblinded.

The BDRM will make decisions that will include, but will not be limited to:

- the determination of whether protocol violations are 'major' or 'minor', or not a protocol violation at all;
- the allocation of patients to analysis sets;
- changes required to the SAP.

After the BDRM and prior to database lock a SAP amendment will be issued if necessary.

## 6.3 General Derivations

- Definition of baseline

Baseline is defined as the last non-missing value (including scheduled and unscheduled assessments) prior to the patient receiving study treatment.

- Incomplete dates

For calculation purposes, incomplete dates will be completed using worst case. Further details are detailed in the relevant sections as required.

- Non-numeric values recorded in a numeric field

In the case where a variable is recorded as “>x”, “≥x”, “<x” or “≤x” in a numeric field, then for analysis purposes a value of x will be taken. Where a range of values is quoted the midpoint of the range will be taken. For example, if a laboratory safety parameter is reported as being below the limit of quantification or < x, the value of the limit will be used in the calculation of summary statistics. The recorded value will be reported in listings.

- Methods for handling withdrawals and missing data

Imputation of any data will be detailed in the relevant sections.

## 6.4 Analysis Sets

The **Enrolled Set** includes all patients who provided informed consent irrespective of whether they received the study treatment.

The “**All Randomised Patients** (RAN)” consists of all patients who were assigned a randomisation number, irrespective of the treatment they received, if any. If this analysis set coincides with the full analysis set, it will be omitted from the tables and listings.

The **Full Analysis Set** (FAS) includes all randomised patients who receive at least one administration of study treatment. Patients will be analysed according to the treatment they are assigned to at randomisation, irrespective of what treatment they actually received.

The **Per-Protocol Set** (PPS) will be a subset of the Full Analysis Set consisting of those patients who:

1. Complete 80% of the study treatment from baseline to day 28 or early termination visit and do not miss more than 3 consecutive days of dosing (or 6 consecutive doses)
2. Have complete MELD score data at baseline and day 28/early termination visit.
3. Do not have major protocol deviations considered having a serious impact on the efficacy results.

All protocol deviations will be assessed and documented on a case-by-case basis prior to the database lock, and major deviations considered having a serious impact on the efficacy results will lead to the relevant patient being excluded from the set. Major protocol deviations considered having a serious impact on the efficacy results include but are not limited to:

- Patients failing any eligibility criteria.

- Patients with treatment deviation.

Protocol deviations other than those specified above may be identified. These will be identified using programmatic data checking where possible, supported by visual review of the data. These deviations will be categorised as either minor or major prior to database lock, at the BDRM prior to unblinding.

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

**Pharmacokinetic (PK) Set (pilot phase)** will consist of those patients who have at least one quantifiable post-dose plasma 15(S)-HEPE concentration. Patients will be analysed according to the treatment actually taken. An evaluable profile allows the determination of one or more PK parameters and will be determined at the discretion of the pharmacokineticist. The Pharmacokinetic set will be used for the summaries of all PK data.

The **Pharmacokinetic (PK) Set (double-blind phase)** will consist of those patients who have at least one quantifiable post-dose plasma 15(S)-HEPE concentration. Patients will be analysed according to the treatment actually taken.

The treatment actually taken will assumed to be the treatment randomised to unless otherwise notified by the sponsor at the time of unblinding.

The list of patients included in the SAF, FAS, PPS and PK (pilot phase) and PK (double-blind phase) set will be agreed prior to breaking the blind for blinded studies, once all study data is available. The definitions for the SAF, FAS and PK (pilot phase) and PK (double-blind phase) set are sufficient to determine the patients included within these analysis sets and so do not require listing and agreeing prior to breaking the blind for blinded studies.

## 6.5 Data presentations

The data will be summarised in tabular form by treatment group apart from disposition of patients, protocol deviations, ‘background and demographic’ data and adverse events which will be summarised by treatment group and overall patients. Treatment labels will be “1000 mg DS102 (BD)”, “Placebo (BD)” and “All Patients” (where applicable).

Only scheduled post-baseline laboratory, electrocardiogram (ECG), nutritional status assessment, cytokeratin18-M30/M65 and vital signs values will be tabulated, post-baseline repeat/unscheduled assessments will be disregarded, although they will be listed and in particular all clinically significant values will be noted (where applicable).

Analysis sets will be summarised using the enrolled set. Study completion/withdrawal and protocol deviations will be summarised using the RAN set. Background and demographic characteristics will be summarised using the FAS. The primary efficacy endpoint will be summarised using the FAS and the PPS. Secondary endpoints will be based on the FAS only. Prior/concomitant medications, administration of study treatment and exposure and safety will be summarised using the SAF. PK (double-blind phase) will be summarised using the PK (double-blind phase) set.

PK (pilot phase) will be based on the PK (pilot phase) set, PK (double-blind phase) will be based on the PK (double-blind phase), safety listings will be based on the SAF set, and all other listings will be based on the enrolled set.

Listings will be sorted by phase, treatment group, patient number and date/time of assessment.

Treatment groups will be presented in the following order “Pilot phase: 1000 mg DS102 (BD)”, “Double-blind phase: 1000 mg DS102 (BD)” and “Placebo (BD)”.

Graphical presentations of the data will also be provided where appropriate.

## 6.6 Disposition of patients

The number and percentage of all patients enrolled, included in the RAN, FAS, PPS, SAF and PK (double-blind phase) analysis sets, who completed the study and prematurely discontinued the study, study duration and treatment duration, will be summarised. The number and percentage of patients will be summarised by their reasons for withdrawal from the study and study treatment. Study duration for each patient will be derived as the number of days between date of randomisation and the date of study completion or the date of early study withdrawal. Treatment duration will be derived as the number of days between 1st administration of study drug and the date of the last administration of study drug.

Eligibility for each of the analysis sets along with reasons for exclusion will be listed. Study completion/withdrawal data will be listed. Consent and visit dates will be listed. Randomisation details will be listed.

Analysis sets presented will be the ones defined in this SAP.

## 6.7 Protocol Deviations

Prior to database lock, Afimmune will review the individual deviations and classify them as major (which includes those described in section 6.3 above) or minor during a BDRM.

Details of all protocol deviations (date, deviation category, specific details and classification of major or minor) and patient eligibility will be listed.

The number and percentage of patients with at least one major protocol deviation will be summarised. Major protocol deviations will be summarised for each major deviation category.

## 6.8 Background and Demographic Characteristics

### 6.8.1 Demography

Demographic characteristics (age, sex, ethnic origin and race), body measurements (height, weight, body mass index (BMI)), alcoholic hepatitis duration, average weekly consumption of alcohol (units per week) and the presence of a history of alcohol abuse for > 6 months (Yes/No) will be summarised by treatment group and overall.

Age at informed consent is captured on the electronic case report form (eCRF).

BMI is calculated as (weight (kg)/height $(m)^2$).

Date of alcoholic hepatitis diagnosis will be recorded. Alcoholic hepatitis duration will be calculated in years as [date of informed consent - date of alcoholic hepatitis

diagnosis+1]/365. Dates will be imputed according to this rule: if the day is missing, day will be imputed as 1st day of the month, if the month is missing, month will be imputed as 1st month of the year.

All patient demographic data including informed consent, AH diagnosis and substance use data will be listed.

### 6.8.2 Medical History

Medical history events will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) dictionary version. The version used will be indicated in the data summaries and listings. The number and percentage of patients will be presented for ongoing conditions and previous conditions separately by system organ class (SOC), and preferred term (PT), where SOC and PT will be presented in decreasing frequency of the total number of patients with medical history events. All events will be listed.

### 6.8.3 HIV, Hepatitis B and Hepatitis C screening

Details of the screen for human immunodeficiency virus (HIV), hepatitis B and hepatitis C will be listed.

### 6.8.4 Liver Ultrasound

Liver ultrasound data will be summarized and listed.

## 6.9 Prior and Concomitant Medications

Medications will be coded using the latest World Health Organization Drug dictionary (WHO Drug) version. The version used will be indicated in the data summaries and listings.

Prior medications are defined as those that started and ended prior to the first administration of study treatment. Medications that are ongoing at the first administration of study treatment or started after time of first administration will be deemed to be concomitant medications. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

The number and percentage of patients taking prior and separately concomitant medications will be summarised by medication class and standardised medication name, where medication class and standardised medication name will be presented in decreasing frequency of the total number of patients with medications. In summary tables, patients taking multiple medications in the same medication class or having the same standardised medication recorded multiple times in the study will be counted only once for that specific medication class and standardised medication name.

Medication data will be listed, and concomitant medications will be flagged.

## 6.10 Administration of Study Treatment and Compliance

The number of doses of study treatment administered will be derived as the (total number of study drug capsules dispensed – total number of study drug capsules returned) over all visits.

Patients compliance with treatment will be measured by the information captured on the patient diary card.

Overall treatment compliance will be derived as a percentage as the (number of doses of study treatment recorded as being administered/N) *100.

Where N= the number of times the patient should have received study treatment=

(Date of treatment withdrawal or day 28/early termination visit – date of baseline visit + 1) x 2

Number of doses of study treatment administered and overall treatment compliance will be summarised.

Study drug dispensing, study drug return and diary card data will be listed.

## 6.11 Primary Endpoint

The model for end-stage liver disease is employed in the evaluation of hepatic function and the assessment of prognosis. MELD is calculated based on variables including the international normalised ratio (INR), serum creatinine and serum bilirubin.

A MELD score ≥ 18 (within 24 hours of presentation) is considered a good predictor of 90-day mortality in patients with AH.

The efficacy primary endpoint of the study is the change in MELD score from baseline to day 28.

For the primary endpoint primary analysis; the null hypothesis ($H_o$: $\mu_1 = \mu_2$) of no difference in change from baseline to day 28 between those patients treated with 1000mg DS102 (BD) and placebo will be rejected in favour of the alternative hypothesis ($H_1$: $\mu_1 \neq \mu_2$) should the probability of the test statistic from observed data occurring if the null hypothesis were true ($\alpha$) be less than 5%.

### 6.11.1 Primary Analysis

Percentage change in MELD score from baseline up to and including day 28 will be assessed by modelling change from baseline with a mixed-model repeated measures (MMRM) analysis, using the FAS, including terms for treatment group, visit, treatment-by-visit interaction as fixed effects and the baseline MELD value as a covariate. The adjusted treatment least squares (LS) means and adjusted mean LS difference between the active dose and placebo will be presented along with 95% confidence intervals (CI) and p-value for the day 28 timepoint. Early termination data will be entered into the model at the next scheduled visit following the date of termination, not at day 28.

F-tests from PROC MIXED will be based on Kenward-Roger's adjusted degrees of freedom. The following variance/covariance matrix structures for the repeated visits within a patient will be assessed: Compound symmetry, 1st order autoregressive, Toeplitz and unstructured. The variance/covariance matrix structure that results in the smallest Akaike's information criterion (AIC), indicating the best model fit will be selected.

Assumptions of normality will be assessed visually using diagnostic plots. Should assumptions of normality not hold the model will be fitted to the change from baseline of log-transformed data. Should the assumptions behind the model still not hold an alternative approach to the analysis will be decided following the BDRM and will be detailed in a SAP amendment.

### 6.11.2 Sensitivity Analysis

The primary analysis will be repeated for the PPS.

Missing MELD data will be imputed using a last observation carried forward approach and the primary analysis will be repeated with the imputed data included.

### 6.11.3 Descriptive summaries and listing

MELD score observed values, absolute change from baseline and percentage change from baseline will be summarised and listed by treatment group and visit.

## 6.12 Secondary Endpoints

### 6.12.1 Change in total bilirubin from baseline to Day 7, 14, 21 and 28

Total bilirubin concentration is a marker of hepatic function.

#### 6.12.1.1 Analysis

Change in total bilirubin from baseline up to and including day 28 will be assessed with an MMRM analysis, using the FAS, including terms for treatment group, visit, treatment-by-visit interaction as fixed effects and the baseline total bilirubin value as a covariate. The adjusted treatment means and adjusted mean difference between the active dose and placebo will be presented along with 95% CI and p-value at days 7, 14, 21 and 28.

The modelling process described in section 6.11.1 will be followed.

#### 6.12.1.2 Descriptive summaries and listing

Covered under section 16.7.

### 6.12.2 Proportion of patients showing a 25% reduction of bilirubin at Day 7, 14, 21 and 28

The proportion of patients showing a 25% reduction of total bilirubin at days 7, 14, 21 and 28 will be compared between treatment groups using a MMRM logistic regression model.

At each visit, patients with >=25% reduction in total bilirubin from baseline will be assigned a value of 1 (indicating 25% reduction achieved) while patients with a <25% reduction will be assigned a value of 0 (indicating 25% reduction not achieved).

The model will include treatment, visit, treatment-by-visit as fixed effects and baseline bilirubin as a covariate.

The variance/covariance matrix structure that results in best model fit will be selected using the process described in section 6.11.1. The adjusted LS estimate for the treatment odds of achieving the endpoint and treatment odds ratio (DS102:Placebo) and corresponding 95% CIs and p-value corresponding to the treatment odds ratio will be presented.

#### 6.12.2.1 Descriptive summaries and listing

The number and percentage of patients showing and patients not showing a 25% reduction of bilirubin at days 7, 14, 21 and 28 will be presented by treatment group.

### 6.12.3 Change in serum Cytokeratin-18 M30/M65 from baseline to Day 7, 14, 21 and 28

Change in serum cytokeratin18-M30/M65 from baseline up to and including day 28 will be assessed with an MMRM analysis, using the FAS, including terms for treatment group, visit and treatment-by-visit interaction as fixed effects and the baseline serum cytokeratin18-M30/M65 value as a covariate. The adjusted treatment means and adjusted mean difference between the active dose and placebo will be presented along with 95% CIs and p-value at days 7, 14, 21 and 28.

The modelling process described in section 6.11.1 will be followed.

#### 6.12.3.1 Descriptive summaries and listing

Serum cytokeratin18-M30/M65 observed values, absolute change from baseline and percentage change from baseline will be listed and summarised by treatment group and visit.

### 6.12.4 Change in AST levels from baseline to Day 7, 14, 21 and 28

Aspartate aminotransferase is liver enzyme and a marker of liver injury.

#### 6.12.4.1 Analysis

Change in AST from baseline up to and including day 28 will be assessed with an MMRM analysis, using the FAS, including terms for treatment group, visit and treatment-by-visit interaction as fixed effects and the baseline AST value as a covariate. The adjusted treatment means and adjusted mean difference between the active dose and placebo will be presented along with 95% CI and p-value at days 7, 14, 21 and 28.

The modelling process described in section 6.11.1 will be followed.

#### 6.12.4.2 Descriptive summaries and listing

Covered under section 16.7.

### 6.12.5 Change in AST:ALT ratio from baseline to Day 7, 14, 21 and 28

Change in AST:ALT from baseline up to and including day 28 will be assessed with an MMRM analysis, using the FAS, including terms for treatment group, visit and treatment-by-visit interaction as fixed effects and the baseline AST:ALT value as a covariate. The adjusted treatment means and adjusted mean difference between the active dose and placebo will be presented along with 95% CI and p-value at days 7, 14, 21 and 28.

The modelling process described in section 6.11.1 will be followed.

#### 6.12.5.1 Descriptive summaries and listing

Covered under section 16.7.

### 6.12.6 Change in MDF score from baseline to Day 7, 14, 21 and 28

The Maddrey discriminant function (MDF) is a measure of liver dysfunction and a method of assessing disease severity.

#### 6.12.6.1 Analysis

Change in MDF score from baseline up to and including day 28 will be assessed with an MMRM analysis, using the FAS, including terms for treatment group, visit and

treatment-by-visit interaction as fixed effects and the baseline MDF value as a covariate. The adjusted treatment means and adjusted mean difference between the active dose and placebo will be presented along with 95% CI and p-value at days 7, 14, 21 and 28.

The modelling process described in section 6.11.1 will be followed.

#### 6.12.6.2 Descriptive summaries and listing

MDF score observed values, absolute change from baseline and percentage change from baseline will be listed and summarised by treatment group and visit.

### 6.12.7 Proportion of patients showing a 25% reduction in MELD score from baseline to Day 7, 14, 21 and 28

The proportion of patients showing at least a 25% reduction in MELD score at days 7, 14, 21 and 28 will be compared between treatment groups using a MMRM logistic regression model.

At each visit, patients with >=25% reduction from baseline will be assigned a value of 1 (indicating 25% reduction achieved) while patients with a <25% reduction will be assigned a value of 0 (indicating 25% reduction not achieved).

The model will include treatment, visit, treatment-by-visit interaction as fixed effects and baseline MELD score as a covariate.

The variance/covariance matrix structure that results in best model fit will be selected using the process described in section 6.11.1.

The adjusted LS estimate for the treatment odds of achieving the endpoint and treatment odds ratio (DS102:Placebo) along with corresponding 95% CIs and p-value (corresponding to the treatment odds ratio) will be presented at days 7, 14, 21 and 28.

#### 6.12.7.1 Descriptive summaries and listing

The number and percentage of patients showing and patients not showing a 25% reduction in MELD score at days 7, 14, 21 and 28 will be presented by treatment group.

### 6.12.8 Change in MELD score from baseline to Day 7, 14 and 21

Estimates for the adjusted treatment LS means and adjusted mean LS difference between the active dose and placebo will be presented along with 95% confidence intervals (CI) and p-value for days 7, 14 and 21 will be obtained from the model fitted in section 6.11.1 and presented in the same table as the primary endpoint.

#### 6.12.8.1 Descriptive summaries and listing

Covered under section 6.11.3.

### 6.12.9 Change in m-SOFA total score from baseline to Day 7, 14, 21 and 28

The m-SOFA score is used in the assessment of disease severity, as well as in predicting mortality.

A score between 0 - 4 will be assigned to the following organ systems parameters: Respiratory, liver, cardiovascular, central nervous system (CNS) and renal. Respiratory function will be measured by SpO2/FiO2, liver function will be classified as scleral icterus or jaundice or no scleral icterus or jaundice, cardiovascular function will check for hypotension, CNS function will be measured using the Glasgow coma score and renal function will be measured by creatinine (mg/dL) levels. A total score

m-SOFA score is derived from the individual scores. For this study, the m-SOFA score is recorded in the eCRF.

#### 6.12.9.1 Analysis

Change in m-SOFA score from baseline up to and including day 28 will be assessed with an MMRM analysis, using the FAS, including terms for treatment group, visit, treatment-by-visit interaction as fixed effects and the baseline m-SOFA value as a covariate. The adjusted treatment means and adjusted mean difference between the active dose and placebo will be presented along with 95% CI and p-value at days 7, 14, 21 and 28.

The modelling process described in section 6.11.1 will be followed.

#### 6.12.9.2 Descriptive summaries and listing

m-SOFA score observed values, absolute change from baseline and percentage change from baseline will be listed and summarised by treatment group and visit.

### 6.12.10 Proportion of patients with a 2-point worsening of m-SOFA from baseline to Day 7, 14, 21 and 28

#### 6.12.10.1 Analysis

The proportion of patients showing a 2-point worsening/increase in m-SOFA score at days 7, 14, 21 and 28 will be compared between treatment groups using a MMRM logistic regression model.

At each visit, patients achieving a >=2-point increase in m-SOFA score from baseline will be assigned a value of 1 (indicating a 2-point worsening) while patients achieving <2-point increase in MELD score will be assigned a value of 0 (indicating not a 2-point worsening).

The model will include treatment, visit, treatment-by-visit interaction and baseline m-SOFA score as a covariate.

The variance/covariance matrix structure that results in best model fit will be selected using the process described in section 6.11.1.

The adjusted LS Means for the treatment odds of achieving the endpoint and treatment odds ratio (DS102:Placebo) along with corresponding 95% CIs and p-value (corresponding to the treatment odds ratio) will be presented at days 7, 14, 21 and 28.

#### 6.12.10.2 Descriptive summaries and listing

The number and percentage of patients showing and patients not showing a two-point worsening in m-SOFA at days 7, 14, 21 and 28 will be presented by treatment group.

### 6.12.11 Change in hepatic encephalopathy as assessed by West Haven Criteria, from baseline to Day 7, 14, 21 and 28

The West Haven Criteria is used to classify the severity of hepatic encephalopathy with a grading of 1 – 4, grade 1 being the least serious with the patient having a trivial lack of awareness to grade 4 in which the patient is in a state of unconsciousness.

#### 6.12.11.1 Analysis

West Haven Criteria data will be analysed using an MMRM ordinal logistic regression model. The model will include treatment, visit and treatment-by-visit interaction as fixed effects and baseline west haven criteria as a covariate.

The variance/covariance matrix structure that results in best model fit will be selected using the process described in section 6.11.1.

Assumptions about the proportionality of odds will also be assessed. Should assumptions not hold an alternative approach to the analysis will be decided following the BDRM and will be detailed in a SAP amendment.

The LS estimate for the treatment odds of achieving the endpoint and treatment odds ratio (DS102:Placebo) along with corresponding 95% CIs and p-value (corresponding to the treatment odds ratio) will be presented at days 7, 14, 21 and 28.

#### 6.12.11.2 Descriptive summaries and listing

West Haven Criteria observed values and absolute change from baseline will be listed and summarised by treatment group and visit.

### 6.12.12 Incidence of acute kidney injury over 28 days

The number and percentage of patients who experienced an acute kidney injury between baseline and day 28 will be summarised by treatment group. The associated 95% Clopper-Pearson exact confidence intervals will also be presented.

Details of treatment measures undertaken for the acute kidney injury will also be summarised.

All acute kidney injury data will be listed.

### 6.12.13 Incidence of variceal haemorrhage, ascites or hepatic encephalopathy over 28 days

The number and percentage of patients who experience a variceal haemorrhage between Baseline and Day 28 will be summarised by treatment group. The associated 95% Clopper-Pearson exact confidence intervals will also be presented.

The number and percentage of patients who have ascites between baseline and day 28 will be summarised by treatment group. The associated 95% Clopper-Pearson exact confidence intervals will also be presented.

Patients who have a hepatic encephalopathy score of 2 or 3 in the data collected for the Child-Pugh score will be classed as having hepatic encephalopathy (Yes). Any patient with a score of 1 will be classed as not having hepatic encephalopathy (No). the number and percentages of patients who have hepatic encephalopathy between baseline and day 28 will be summarised by treatment group. The associated 95% Clopper-Pearson exact confidence intervals will also be presented.

All variceal haemorrhage and ascites data will be listed. Hepatic encephalopathy will be included into the Child-Pugh listing.

## 6.13 Exploratory Endpoints

### 6.13.1 Survival at day 7, 14, 21, 28 and 90

Survival time will be derived as:

(Death date/last date patient known to be alive – date of randomisation + 1).

Survival time will be analysed with a Cox proportional hazards model including covariates for treatment group and baseline MELD score. Tied observations will be

handled using the Breslow-Henshaw method. The assumption of proportional hazards will be assessed visually using the log-log plot.

Estimates for the hazard ratio (DS102:Placebo), associated 95% CI and p-values will be presented.

Estimates of survival rate and associated 95% CI at days 7, 14, 21, 28 and 90 will be presented for each treatment group.

Kaplan-Meier plot of the probability of survival against time (days) will be presented for each treatment group.

### 6.13.2 Change in GT from baseline to day 7, 14, 21 and 28

Gamma glutamyl transferase is a liver enzyme indicative of liver dysfunction and alcohol intake.

#### 6.13.2.1 Analysis

Change in GT from baseline up to and including day 28 will be assessed with an MMRM analysis, using the FAS, including terms for treatment group, visit, treatment-by-visit as fixed effects and the baseline GT value as a covariate. The adjusted treatment means and adjusted mean difference between the active dose and placebo will be presented along with 95% CI and p-value for the day 7, 14, 21 and 28 timepoint.

The modelling process described in section 6.11.1 will be followed.

#### 6.13.2.2 Descriptive summaries and listing

Covered under section 16.7.

### 6.13.3 Change in ALT from baseline to day 7, 14, 21 and 28

Alanine aminotransferase is liver enzyme and a marker of liver injury.

#### 6.13.3.1 Analysis

Change in ALT from baseline up to and including day 28 will be assessed with an MMRM analysis, using the FAS, including terms for treatment group, visit, treatment-by-visit as fixed effects and the baseline ALT value as a covariate. The adjusted treatment means and adjusted mean difference between the active dose and placebo will be presented along with 95% CI and p-value for the day 7, 14, 21 and 28 timepoint.

The modelling process described in section 6.11.1 will be followed.

#### 6.13.3.2 Descriptive summaries and listing

Covered under section 16.7.

### 6.13.4 Change in Child-Pugh score from baseline to day 7, 14, 21 and 28

The Child-Pugh score is a means of assessing the severity of chronic liver disease, including cirrhosis, based on five clinical parameters (bilirubin, albumin, INR, ascites and hepatic encephalopathy) scored on a scale of 1 to 3. A total score is which indicates the severity and prognosis of chronic liver disease is then derived.

#### 6.13.4.1 Analysis

Change in Child-Pugh score from baseline up to and including day 28 will be assessed with an MMRM analysis, using the FAS, including terms for treatment group, visit, treatment-by-visit as fixed effects and the baseline Child-Pugh score as a covariate.

The adjusted treatment means and adjusted mean difference between the active dose and placebo will be presented along with 95% CI and p-value for the day 7, 14, 21 and 28 timepoint.

The modelling process described in section 6.11.1 will be followed.

#### 6.13.4.2 Descriptive summaries and listing

Child-Pugh score observed values, absolute change from baseline and percentage change from baseline will be listed and summarised by treatment group and visit.

### 6.13.5 Change in APACHE-II score from baseline to day 7, 14 , 21 and 28

The acute physiologic and chronic health evaluation II score will assess patients for the presence of multiple organ dysfunction and predict mortality by generating a point score ranging from 0 to 71 based on twelve physiologic variables, age and underlying health.

#### 6.13.5.1 Analysis

Change in APACHE-II score from baseline up to and including day 28 will be assessed with an MMRM analysis, using the FAS, including terms for treatment group, visit, treatment-by-visit as fixed effects and the baseline APACHE-II value as a covariate. The adjusted treatment means and adjusted mean difference between the active dose and placebo will be presented along with 95% CI and p-value for the day 7, 14, 21 and 28 timepoints.

The modelling process described in section 6.11.1 will be followed.

#### 6.13.5.2 Descriptive summaries and listing

APACHE-II score observed values, absolute change from baseline and percentage change from baseline will be listed and summarised by treatment group and visit.

### 6.13.6 Change in Lille score from baseline to day 7, 14, 21 and 28

The Lille score is a composite score which predicts mortality in patients with AH who are not responding to steroid therapy. It is based on age, albumin, bilirubin (initial), bilirubin (day 7), creatinine and prothrombin time. A score of > 0.45 identifies 75% of deaths, a score of > 0.45 predicts a 6-month survival of 25% and a score of < 0.45 predicts survival of 85%.

#### 6.13.6.1 Analysis

Change in Lille score from baseline up to and including day 28 will be assessed with an MMRM analysis, using the FAS, including terms for treatment group, visit, treatment-by-visit as fixed effects and the baseline Lille score as a covariate. The adjusted treatment means and adjusted mean difference between the active dose and placebo will be presented along with 95% CI and p-value for the day 7, 14, 21 and 28 timepoints.

The modelling process described in section 6.11.1 will be followed.

#### 6.13.6.2 Descriptive summaries and listing

Lille score observed values, absolute change from baseline and percentage change from baseline will be listed and summarised by treatment group and visit.

### 6.13.7 Combination of change of MELD score from baseline, premature treatment terminations and mortality

A 5-level ordinal variable combining change of MELD score from baseline, premature treatment terminations and mortality will be derived.

Each patient will be allocated to the lowest/worst level that occurred.

Level 1: death within 28 days using survival time derived in section 6.13.1

Level 2: death within 90 days using survival time derived in section 6.13.1

Level 3: early termination because of safety issues or lack of efficacy

Level 4: no improvement in MELD score at day 28 compared to baseline (classed as less than 25% reduction in MELD score from baseline to day 28).

Level 5: improvement in MELD score at day 28 compared to baseline (classed as greater than or equal to a 25% reduction in MELD score baseline to day 28).

Patients who are lost to follow up within 28 days and therefore do not have a day 28 MELD score will be allocated to level 4 or 5 depending on their imputed result at day 28 based on the model in section 6.11.1 under a missing at random (MAR) assumption.

#### 6.13.7.1 Analysis

The 5-level ordinal variable will be analysed using an ordinal logistic regression model. The model will include treatment as a fixed effect and baseline MELD score as a covariate.

Assumptions about the proportionality of odds will also be assessed. Should assumptions not hold, then the treatment odds ratios for the individual cumulative levels of the variable will be presented..

The adjusted LS estimate for the treatment odds and treatment odds ratio (DS102:Placebo) along with corresponding 95% CI and p-value (corresponding to the treatment odds ratio) will be presented.

#### 6.13.7.2 Descriptive summaries and listing

The 5-level ordinal variable be listed and summarised by treatment group and visit.

## 6.14 Multiplicity

All secondary endpoints and the supportive analyses will be considered as descriptive evidence of efficacy and will be analysed without any procedures to account for multiple comparisons.

## 6.15 Pharmacokinetics

Pharmacokinetics analyses for the pilot and double-blind phases of the study will be conducted as detailed in Appendix 1 Pharmacokinetic Data Analysis Plan (PKAP). Only outputs relating to the double-blind phase will be produced as part of this SAP. Note the double-blind phase is referred to as treatment phase in the PKAP.

## 6.16 Safety Evaluation

### 6.16.1 Adverse Events

Adverse events (AEs) will be coded using the latest MedDRA dictionary version. The version used will be indicated in the data summaries and listings.

A treatment-emergent adverse event (TEAE) is defined as an AE that started on or after the start of the administration study treatment. If adverse event dates are incomplete and it is not clear whether the adverse event was treatment-emergent, it will be assumed to be treatment-emergent.

Any AE commencing after the last administration of study treatment may be considered treatment emergent.

A summary table by treatment and overall will present the following:

- TEAEs (events and patients).
- Serious TEAEs (events and patients).
- Serious study treatment related TEAEs (events and patients).
- TEAEs by pattern (intermittent/continuous/single event) (events and patients).
- TEAEs by severity (mild/moderate/severe) (events and patients).
- TEAEs by relationship to study treatment (events and patients).
- TEAEs leading to withdrawal from study (patients only).
- TEAEs leading to discontinuation of study treatment (patients only).
- Study treatment related TEAEs leading to discontinuation of study treatment (patients only).
- TEAEs leading to death (patients only).

In the above summaries, if a patient experienced more than one TEAE, the patient will be counted once using the most related event for the “by relationship to study treatment” and “related to study treatment” summaries and at the worst severity for the “by severity” summary. If a patient experienced more than one TEAE, the patient will be counted once for each pattern recorded. For summaries at the patient level, the number and percent of patients will be presented.

The above summary table will be presented for the pilot and double-blind phases.

The following tables will be presented:

- TEAEs by System Organ Class (SOC) and Preferred Term (PT).
- TEAEs by PT.
- TEAEs by SOC, PT and severity.
- TEAEs by SOC, PT and relationship to study treatment (related/ not related).
- Serious TEAEs by SOC and PT
- TEAEs leading to withdrawal by SOC and PT

For all of the above, SOC and PT will be presented in decreasing frequency of the total number of patients with TEAEs. Number of events and number and percentage of patients will be presented.

Further details of the above four tables are given below:

1. If a patient experienced more than one TEAE the patient will be counted once for each SOC and once for each PT.
2. If a patient experienced more than one TEAE, the patient will be counted once for each PT.
3. If a patient experienced more than one TEAE, the patient will be counted once for each SOC and once for each PT at the worst severity.
4. If a patient experienced more than one TEAE, the patient will be counted once for each SOC and once for each PT using the most related event.

Adverse event data will be listed in full and this will also include a treatment emergent flag, the time of onset and cessation of event percentage to first dosing of study treatment and duration of AE.

## 6.17 Clinical Laboratory Evaluation

Observed values and change from baseline in haematology, biochemistry, urinalysis, and coagulation assessments will be summarised over time. If the test results are reported in categorical format, the results will be summarised by patient counts and percentage for each category. Percentage change will be included on the biochemistry summary table.

Ratio of AST to ALT will be derived and presented along with the other assessments.

Each haematology, biochemistry, urinalysis and coagulation parameter will be classed as low, normal, high, missing based on the reference ranges. Shift tables in relation to the normal range from baseline over time will be presented.

Haematology, biochemistry, urinalysis and coagulation data will be listed separately including change from baseline, reference ranges flagging all out of range values and their clinical significance.

Listings of clinically significant haematology, biochemistry, urinalysis and coagulation laboratory measurements recorded throughout the study will be provided.

## 6.18 Vital Signs

Vital sign observed values and change from baseline by parameter (unit) will be summarised over time.

In addition, 'substantial' changes from baseline will be categorised as follows: change from baseline in systolic/diastolic blood pressure (systolic BP [<-40 mmHg, >+40 mmHg], diastolic BP [<-20 mmHg, >+20 mmHg]) and heart rate [<-30 bpm, >+30 bpm]). The number and percentage of patients with changes from baseline as categorised above will be summarised separately for positive and negative changes over time and at any post-baseline time point.

All vital sign data will be listed including change from baseline and flags for substantial changes from baseline, reference ranges flagging all out of range values and their clinical significance.

A listing of clinically significant vital signs recorded throughout the study will be provided.

## 6.19 Electrocardiography

The overall interpretation of the ECG (Normal, Abnormal Not Clinically Significant (NCS), and Abnormal Clinically Significant (CS)) will be summarised over time.

All ECG data will be listed.

## 6.20 Physical Examination

Details of timings of physical examinations will be listed.

## 6.21 Pregnancy test

Pregnancy test details will be listed.

## 6.22 Exploratory Blood Collection

Exploratory blood collection data will be listed.

## 6.23 Liver Histopathology

Liver Biopsy History and Liver histopathology data including Non-Alcoholic Steatohepatitis (NASH) activity grading and fibrosis staging will be summarised and listed.

## 6.24 Nutritional Status Assessment

Bedside subjective global assessment will be scored as (0,1,2 and 3). Patients will be classified into the following categories: well nourished (0), mild malnutrition (1), moderate malnutrition (2) and severe malnutrition (3).

BMI will be recorded on the eCRF.

Nutritional status assessment data will be summarised and listed.

## 6.25 Changes from the Protocol Planned Analysis

The study protocol refers to a total population set however no analyses will be performed using this set because screen failures will not be databased.

The study protocol section 5.3 states that exploratory endpoints for APACHE-II and Lille scores will be change from baseline to Day 7, 14 and 28, this SAP is also including change from baseline to Day 21 as an exploratory outcome to be in-line with other outcome measures.

The study protocol section 5.4 states that SUSARs will be one of the safety endpoints, reporting of these is not covered by this SAP.

The study protocol section 12.9.1 refers to calculation and reporting of PK parameters for the double-blind phase. These will not be carried out as part of the PKAP and will not be reported as part of this SAP.

# 7 APPENDIX 1 – PHARMOCOKINETIC DATA ANALYSIS PLAN


Afm091318_PK DAP_V01.docx


Afm091318_PK DAP TABLES_V01.xlsx


Afm091318_PK DAP FIGURES_V01.xlsx

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# PHARMACOKINETIC DATA ANALYSIS PLAN

## PKPD Strategies Project Afm091318a

# Pharmacokinetic Analysis of Plasma Free and Total 15(S)-HEPE Concentrations from Study DS102A-05-AH1 Following Twice-daily Oral Administration of 1000 mg or 2000 mg DS102 in Patients with Severe Acute Decompensated Alcoholic Hepatitis

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Study DS102A-05-AH1: "A Randomised, Double-Blind, Placebo-Controlled, Phase II Study to Assess the Efficacy and Safety of Orally Administered DS102 in Patients with Severe Acute Decompensated Alcoholic Hepatitis", Version 4.0, 01 August 2018

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# Signature Page

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# Table of Contents

# Abbreviations

| | |
|---|---|
| %Extrap | Percentage of $AUC_{inf}$ obtained by extrapolation |
| ALQ | Above the upper limit of assay quantification |
| $AUC_{inf}$ | Area under the plasma concentration-time curve from time 0 extrapolated to infinite time |
| $AUC_t$ | Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration |
| $AUC_{tau}$ | Area under the plasma concentration-time curve over a dosage interval |
| BD | Twice daily administration |
| BLQ | Below the limit of assay quantification |
| $C_{avg}$ | Average plasma concentration over a dosage interval |
| $C_{last}$ | Last quantifiable plasma concentration |
| $C_{max}$ | Maximum observed plasma concentration |
| CV% | Percent coefficient of variation |
| D | Dose |
| DAP | Data analysis plan |
| dp | Number of decimal points |
| DSMB | Data safety monitoring board |
| Flucp | Fluctuation at pharmacokinetic steady-state |
| GeoMean | Geometric mean |
| $K_{el}$ | Apparent first-order terminal elimination rate constant |
| LC/MS-MS | Liquid chromatography tandem mass spectrometry |
| PC | CDISC-compliant concentration dataset |
| PK | Pharmacokinetic(s) |
| PP | CDISC-compliant pharmacokinetic dataset |
| $R_{ac}$ | Accumulation ratio at pharmacokinetic steady-state |
| SD | Standard deviation |
| SOP | Standard operating procedure |
| $t_{½}$ | Apparent first-order terminal elimination half-life |
| $t_{last}$ | Time to reach the last quantifiable plasma concentration |
| $t_{max}$ | Time of maximum observed plasma concentration |
| $t_{ss}$ | Time to achieve pharmacokinetic steady state |
| 15(S)-HEPE EE | 15-hydroxy eicosapentaenoic acid ethyl ester |

# Objectives and Rationale

## Overview of Study and Planned Analysis

The objectives of this randomized, double-blind, placebo-controlled, Phase II study are as follows.

*Efficacy Objective:*

• To compare the efficacy of orally administered DS102 versus placebo, in the treatment of adult patients with severe acute decompensated Alcoholic Hepatitis (AH).

*Safety Objective:*

• To compare the safety of orally administered DS102 versus placebo, in the treatment of adult patients with severe acute decompensated AH.

*Pharmacokinetic Objective:*

• To evaluate the pharmacokinetics (PK) of 15(S)-HEPE following orally administered DS102 capsules, in six adult patients with AH in an initial pilot phase of the study, followed by trough level assessment of 15(S)-HEPE in all study participants.

## Scope

The 3rd objective listed above is the focus of this data analysis plan. This data analysis project covers data receipt and handling, pharmacokinetic data analysis, data display preparation, and summarization of the plasma free and total 15(S)-HEPE concentrations from the Pilot phase of this study. *Note: Although included in the Mock Displays, data display preparation for the Treatment phase of this study is outside the scope of this analysis plan and will be conducted separately.*

## Compliance

This analysis is to be done in compliance with current PKPD Strategies Standard Operating Procedures (SOPs) and all applicable regulations and guidances.

# Protocol Summary

## Study Design

This is a multicenter, double blind, placebo controlled, 2-arm parallel group comparison Phase 2 study. In an initial pilot phase, six patients will receive open label treatment with DS102 1000 mg orally twice daily (BD) within 30 minutes after a meal for 28 days. After the pilot phase, all patients will either receive 1000 mg DS102 (BD) or placebo (BD), in addition to standard of care therapy, within 30 minutes after a meal for 28 days in the two treatment groups of 60 patients each.

DS102 exhibits a $t_{max}$ of approximately 4 to 8 hours and a short elimination half-life ($t_{½}$) of approximately 2 hours. High pharmacokinetic (PK) variability has been observed following both single and multiple dosing, and DS102 did not exhibit a linear correlation between increasing dose and resultant systemic exposure. Co-administration with food increased DS102 bioavailability, although there was no difference in bioavailability between normal and high fat diet fed conditions.

## Subject Population

Subjects in this study will be male or female patients, aged 18 years or older, with evident severe acute decompensated alcoholic hepatitis.

## Treatment Administration

DS102 will be provided as a capsule containing 500 mg of 15(S)-HEPE EE with 5% w/w of colloidal silicon dioxide as viscosity modifier. In the open label pilot phase, 2000 mg (1000 mg BD) will be orally administered as 2 capsules within 30 minutes after a meal for 28 days. In the double-blind phase of the study either 1000 mg (BD) or placebo (BD) will be orally administered, in addition to standard of care therapy, within 30 minutes after a meal for 28 days. Treatment label will be 1000 mg DS102 BD.

After the completion of the open-label phase of the study the DSMB will evaluate the safety and pharmacokinetic data and might recommend a dose adjustment for the double blind randomised phase of the study. The decision to proceed with the double-blind phase of this study will be determined by the DSMB following review of the data from the pilot phase.

Available information on concomitant standard-of-care treatment or medications used to treat comorbidities during the trial will be assessed for potential impact on observed pharmacokinetic results.

## Sampling Design

During the study, 8 visits to the clinic are scheduled after the screening visit (Visit 1): one at the start of the comparative treatment period (Baseline/Visit 2) and six in the comparative treatment period (Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, Visit 8/Day 28 or Early Termination).

Blood samples for PK analysis will be collected via direct venipuncture as per the Study Flow Chart at Visit 2/Baseline, Visit 3/Day 3, Visit 4/Day 5, Visit 5/Day 7, Visit 6/Day 14, Visit 7/Day 21, and Visit 6/Day 28/Early Termination. Trough plasma samples will be obtained from all patients (pilot and double-blind phases) prior to first daily dose on the indicated days. Additional post-dose serial plasma samples will be obtained from the 6 patients of the Pilot phase for full PK characterization on Days 0 and 7 at 0.5, 1, 2, 3, 4, 6, 7, 8, 10, and 12 (before next dose) hours post-dose. A 1 mL blood sample will be taken at each time point. Following centrifugation, plasma samples will be split in two and a back-up sample will be handled as described in the laboratory manual.

Plasma free and total 15(S)-HEPE concentrations will be determined by Charles River Laboratories (Edinburgh Ltd) using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods.

# Input Data Handling

## Evaluability Criteria

The **Pharmacokinetic (PK) Set** will consist of those patients who have at least one quantifiable post-dose plasma 15(S)-HEPE concentration. Patients will be analysed according to the treatment actually taken. An evaluable profile allows the determination of one or more PK parameters and will be determined at the discretion of the pharmacokineticist. The Pharmacokinetic set will be used for the summaries of all PK data.

## Off-time Sample Times

Actual sampling times will be used for all analyses. Nominal time will be used to tabulate plasma 15(S)-HEPE concentrations by time and for all figures.

## Out of Range Data

Plasma 15(S)-HEPE concentration-time data will be reviewed to confirm all reported values are valid and are within the lower and upper limits of assay quantitation. Values below or above these limits will be identified as BLQ and ALQ, respectively. BLQ values will be treated either as zero for concentrations prior to the first Cmax or as missing values in all other pharmacokinetic analyses and data presentations. ALQ values will be treated as missing in all analyses and presentations.

## Detectable Pre-dose Concentrations

Plasma 15(S)-HEPE concentration data will be reviewed for detectable pre-dose concentrations. Detectable values will be handled according to procedures described in applicable PKPD Strategies SOPs.

## Outlying Data

Plasma 15(S)-HEPE concentration data will be reviewed for outlying or unexpected post-dose concentrations. Questionable values will be queried for possible reassay, and may be used or excluded at the discretion of the pharmacokineticist with concurrence from the sponsor.

## Missing Data

Plasma 15(S)-HEPE concentration data will be reviewed for missing concentrations. Reasons for missing values will be assessed and followed up accordingly.

For any known hemolyzed plasma samples, consistency of the sample concentration with that subject's concentration-time profile will be assessed. If considered inconsistent by the pharmacokineticist, the affected profile may be analyzed either without the concentration for the sample in question or analyzed with and without, whichever is more appropriate at the discretion of the pharmacokineticist with concurrence from the sponsor.

## Clinical Observations

If available, clinical observations pertinent to the pharmacokinetic analysis such as body weight, BMI, emesis or concomitant medications may be assessed for potential impact on the outcome of the analysis.

## Input Datafile Creation

### Source

Data will be obtained directly from the Sponsor or their designee.

### Format

Concentration and associated elapsed time (sampling time minus prior dosing time) results will be received in an Excel-readable file format and will be identified by Study Period, Treatment, Subject, and Nominal Time. Data format has not been prespecified, and will be used as received from the Sponsor or their designee.

### Precision

Data precision has not been prespecified, and will be used as received. Precision of reported results will follow applicable PKPD Strategy SOPs.

### Units

Time is to be reported in hours and plasma 15(S)-HEPE concentrations are to be reported in ng/mL.

# Data Analysis

## Planned Pharmacokinetic Assessments

Plasma free and total 15(S)-HEPE concentration-time results will be processed according to standard noncompartmental pharmacokinetic analysis procedures using actual sampling times. The software programs to be used are Phoenix WinNonlin Version 6.4 (Certara Corporation, USA), Microsoft Office Excel 2010, and Microsoft Office Word 2010.

Where feasible, the following non-compartmental PK parameters will be generated:

| Parameter | Definition | Units | Precision |
|---|---|---|---|
| %Extrap | Percentage of $AUC_{inf}$ obtained by extrapolation | % | 1 dp |
| $AUC_{inf}$ | Area under the plasma concentration-time curve from time 0 extrapolated to infinite time | ng•hr/mL | 1 dp |
| $AUC_t$ | Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration | ng•hr/mL | 1 dp |
| $AUC_{tau}$ | Area under the plasma concentration-time curve over a dosage interval | ng•hr/mL | 1 dp |
| $C_{avg}$ | Average plasma concentration over a dosage interval | ng/mL | 3 dp |
| $C_{last}$ | Last quantifiable plasma concentration | ng/mL | 3 dp |
| $C_{max}$ | Maximum observed plasma concentration | ng/mL | 3 dp |
| Flucp | Fluctuation at pharmacokinetic steady-state | % | 1 dp |
| $K_{el}$ | Apparent first-order terminal elimination rate constant | 1/hr | 4 dp |
| $R_{ac}$ | Accumulation ratio at pharmacokinetic steady-state | % | 1 dp |
| $t_{½}$ | Apparent first-order terminal elimination half-life | hr | 1 dp |
| $t_{last}$ | Time to reach the last quantifiable plasma concentration | hr | 1 dp |
| $t_{max}$ | Time of maximum observed plasma concentration | hr | 1 dp |
| $t_{ss}$ | Time to achieve pharmacokinetic steady state | hr | 1 dp |

## Planned Statistical Assessments

Descriptive statistics will be used to summarize plasma free and total 15(S)-HEPE concentrations and resultant pharmacokinetic parameters by treatment across study subjects. Summary statistics will include number of non-missing observations, geometric mean, mean, standard deviation, coefficient of variation, minimum, median, and maximum as appropriate.

# Analysis Output/Summarization

Data displays for patients from the pilot phase and the double-blind phase of the study will be presented separately. Should the study be discontinued after the pilot phase, the listings described in the sections below will be produced for the pilot phase only.

## Summarization

Pharmacokinetic analysis methods, results, and conclusions will be summarized in a separate PK Report, with pertinent information included in the clinical study report. Results for plasma 15(S)-HEPE concentrations and 15(S)-HEPE pharmacokinetic parameters will be summarized and discussed relative to differences between treatments and prior study results. Conclusions related to the study objectives will be presented.

## Datasets

Plasma 15(S)-HEPE concentration time data used for input into the PK analysis will be provided as a CDISC-compliant PC dataset. Resultant 15(S)-HEPE PK parameter results will be provided as a CDISC-compliant PP dataset.

## Data Displays

Planned data displays are listed as follows.

**TABLES**

**In-Text:**

**Table A**. Descriptive Statistics for Plasma Free 15(S)-HEPE Pharmacokinetic Results for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase).

**Table B**. Descriptive Statistics for Plasma Total 15(S)-HEPE Pharmacokinetic Results for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase).

**End-of-Text:**

**Table 1.** Individual Plasma Free 15(S)-HEPE Concentrations (ng/mL) and Descriptive Statistics for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Day 0)

**Table 2.** Individual Plasma Free 15(S)-HEPE Concentrations (ng/mL) and Descriptive Statistics for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Day 7)

**Table 3.** Individual Plasma Free 15(S)-HEPE Concentrations (ng/mL) and Descriptive Statistics for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Troughs)

**Table 4.** Individual Plasma Total 15(S)-HEPE Concentrations (ng/mL) and Descriptive Statistics for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Day 0)

**FIGURES**

**In-Text:**



**End-of-Text:**

**Figure 4.** Individual Subject-overlay Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Day 7).

**Figure 5.** Individual Subject-overlay Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Trough Concentrations).

**Figure 6.** Individual Subject-overlay Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Trough Concentrations).

**APPENDICES**

**Appendix Figures 1.1-1.6.** Individual Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (semilogarithmic scale only) and Terminal Phase Regressions, by Subject for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1- Pilot Phase, Days 0 and 7).

**Appendix Figures 1.7-1.12.** Individual Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (semilogarithmic scale only) and Terminal Phase Regressions, by Subject for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1- Pilot Phase, Days 0 and 7).

**DATA DISPLAYS FOR TREATMENT STUDY-PHASE (prepared separately)**

**Table x1.** Descriptive Statistics for Plasma Free 15(S)-HEPE Concentrations (ng/mL) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase).

**Table x2.** Descriptive Statistics for Plasma Total 15(S)-HEPE Concentrations (ng/mL) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase).

**Table x3.** Individual Plasma Free 15(S)-HEPE Concentrations (ng/mL) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase).

**Table x4.** Individual Plasma Total 15(S)-HEPE Concentrations (ng/mL) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase).

**Figure x1.** Mean (+/-SD) Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase).

**Figure x2.** Mean (+/-SD) Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase).

**Figure x3.** Individual Subject-overlay Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase).

**Figure x4.** Individual Subject-overlay Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase).

## Mock Data Displays

Content and layout of the planned tables and figures are represented in the mock displays (provided separately from this document). Final format and content may differ from these displays depending on the outcome of the data analysis.

**PK Mock Data Displays - TABLES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

## TABLES

### In-Text:



### End-of-Text:



### DATA DISPLAYS FOR TREATMENT STUDY-PHASE (prepared separately)

**PK Mock Data Displays - TABLES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**
Note: Parameters shown without subscripting

**A** Free
**B** Total

| Day 0 | Pharmacokinetic Parameter | | | | | | |
|---|---|---|---|---|---|---|---|
| Statistic | tmax | Cmax | AUCt | AUCtau | AUCinf | %Extrap | t½ |
| n | | | | | | | |
| GeoMean | | | | | | | |
| Mean | | | | | | | |
| SD | | | | | | | |
| CV% | | | | | | | |
| Minimum | | | | | | | |
| Median | | | | | | | |
| Maximum | | | | | | | |

| Day 7 | Pharmacokinetic Parameter | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Subject | tmax | Cmax | AUCtau | Cavg | tss | Rac | Flucp | t½ |
| n | | | | | | | | |
| GeoMean | | | | | | | | |
| Mean | | | | | | | | |
| SD | | | | | | | | |
| CV% | | | | | | | | |
| Minimum | | | | | | | | |
| Median | | | | | | | | |
| Maximum | | | | | | | | |

**PK Mock Data Displays - TABLES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**1** Free
**4** Total

| | Elapsed Time Post-dose (hr) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject | 0 | 0.5 | 1 | 2 | 3 | 4 | 6 | 7 | 8 | 10 | 12 |
| 1 | | | | | | | | | | | |
| 2 | | | | | | | | | | | |
| 3 | | | | | | | | | | | |
| 4 | | | | | | | | | | | |
| 5 | | | | | | | | | | | |
| 6 | | | | | | | | | | | |
| | | | | | | | | | | | |
| n | | | | | | | | | | | |
| GeoMean | | | | | | | | | | | |
| Mean | | | | | | | | | | | |
| SD | | | | | | | | | | | |
| CV% | | | | | | | | | | | |
| Minimum | | | | | | | | | | | |
| Median | | | | | | | | | | | |
| Maximum | | | | | | | | | | | |

**PK Mock Data Displays - TABLES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**2** Free
**5** Total

| | Elapsed Time Post-dose (hr) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject | 0 | 0.5 | 1 | 2 | 3 | 4 | 6 | 7 | 8 | 10 | 12 |
| 1 | | | | | | | | | | | |
| 2 | | | | | | | | | | | |
| 3 | | | | | | | | | | | |
| 4 | | | | | | | | | | | |
| 5 | | | | | | | | | | | |
| 6 | | | | | | | | | | | |
| | | | | | | | | | | | |
| n | | | | | | | | | | | |
| GeoMean | | | | | | | | | | | |
| Mean | | | | | | | | | | | |
| SD | | | | | | | | | | | |
| CV% | | | | | | | | | | | |
| Minimum | | | | | | | | | | | |
| Median | | | | | | | | | | | |
| Maximum | | | | | | | | | | | |

**PK Mock Data Displays - TABLES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**3** Free
**6** Total

| Subject | Day 0, 0 hr | Day 0, 12 hr | Day 3 | Day 5 | Day 7 | Day 14 | Day 21 | Day 28 |
|---|---|---|---|---|---|---|---|---|
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
| 6 | | | | | | | | |
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| n | | | | | | | | |
| GeoMean | | | | | | | | |
| Mean | | | | | | | | |
| SD | | | | | | | | |
| CV% | | | | | | | | |
| Minimum | | | | | | | | |
| Median | | | | | | | | |
| Maximum | | | | | | | | |

**PK Mock Data Displays - TABLES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**
Note: Parameters shown without subscripting

| Day 0 | Pharmacokinetic Parameter | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Subject | tmax | Cmax | tlast | Clast | AUCt | AUCtau | AUCinf | %Extrap | Kel | t½ |
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| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | | | | | | | | | | |
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| n | | | | | | | | | | |
| GeoMean | | | | | | | | | | |
| Mean | | | | | | | | | | |
| SD | | | | | | | | | | |
| CV% | | | | | | | | | | |
| Minimum | | | | | | | | | | |
| Median | | | | | | | | | | |
| Maximum | | | | | | | | | | |

**PK Mock Data Displays - TABLES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**
Note: Parameters shown without subscripting

| Day 7 | Pharmacokinetic Parameter | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject | tmax | Cmax | tlast | Clast | AUCt | AUCtau | Cavg | tss | Rac | Flucp | Kel | t½ |
| 1 | | | | | | | | | | | | |
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| 6 | | | | | | | | | | | | |
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| n | | | | | | | | | | | | |
| GeoMean | | | | | | | | | | | | |
| Mean | | | | | | | | | | | | |
| SD | | | | | | | | | | | | |
| CV% | | | | | | | | | | | | |
| Minimum | | | | | | | | | | | | |
| Median | | | | | | | | | | | | |
| Maximum | | | | | | | | | | | | |

**PK Mock Data Displays - TABLES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**x1** Free
**x2** Total

| Statistic | Day 0 | Day 3 | Day 5 | Day 7 | Day 14 | Day 21 | Day 28 |
|---|---|---|---|---|---|---|---|
| n | | | | | | | |
| GeoMean | | | | | | | |
| Mean | | | | | | | |
| SD | | | | | | | |
| CV% | | | | | | | |
| Minimum | | | | | | | |
| Median | | | | | | | |
| Maximum | | | | | | | |

**PK Mock Data Displays - TABLES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**x3** Free
**x4** Total

| Subject | Day 0 | Day 3 | Day 5 | Day 7 | Day 14 | Day 21 | Day 28 |
|---|---|---|---|---|---|---|---|
| 1 | | | | | | | |
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**PK Mock Data Displays - FIGURES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**In-Text:**

**Figure A** Mean (+/-SD) Day-overlay Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Days 0 and 7)

**Figure B** Mean (+/-SD) Day-overlay Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Days 0 and 7)

**Figure C** Mean (+/-SD) Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Trough Concentrations)

**Figure D** Mean (+/-SD) Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Trough Concentrations)

**End-of-Text:**

**Figure 1** Individual Subject-overlay Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Day 0)

**Figure 2** Individual Subject-overlay Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Day 0)

**Figure 3** Individual Subject-overlay Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Day 7)

**Figure 4** Individual Subject-overlay Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Day 7)

**Figure 5** Individual Subject-overlay Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Trough Concentrations)

**Figure 6** Individual Subject-overlay Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Pilot Phase, Trough Concentrations)

**APPENDICES**

**App Fig 1-6** Individual Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (semilogarithmic scale only) and Terminal Phase Regressions, by Subject for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1- Pilot Phase, Days 0 and 7)

**App Fig 7-12** Individual Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (semilogarithmic scale only) and Terminal Phase Regressions, by Subject for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1- Pilot Phase, Days 0 and 7)

**DATA DISPLAYS FOR TREATMENT STUDY-PHASE (prepared separately)**

**Figure x1** Mean (+/-SD) Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase)

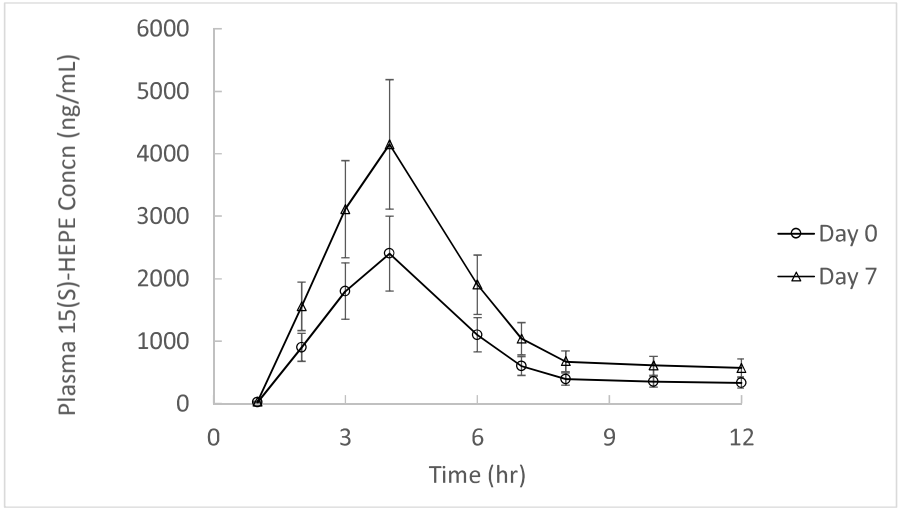
**Figure x2** Mean (+/-SD) Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase)

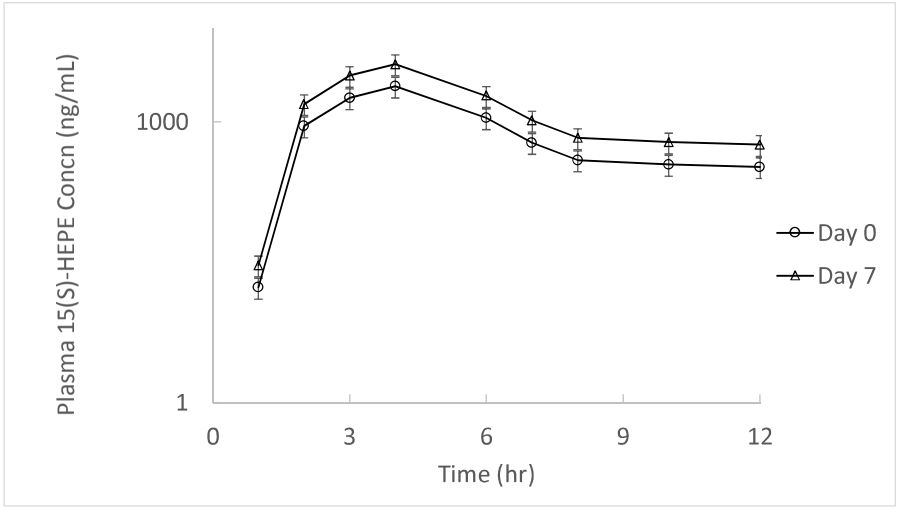
**Figure x3** Individual Subject-overlay Plasma Free 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase)

**Figure x4** Individual Subject-overlay Plasma Total 15(S)-HEPE Concentrations (ng/mL) versus Time (linear and semilogarithmic scales) for 1000 mg BD DS102 Administered Orally Twice-daily to Patients with Alcoholic Hepatitis (Protocol DS102A-05-AH1 – Treatment Phase)

**PK Mock Data Displays - FIGURES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**A** Free
**B** Total



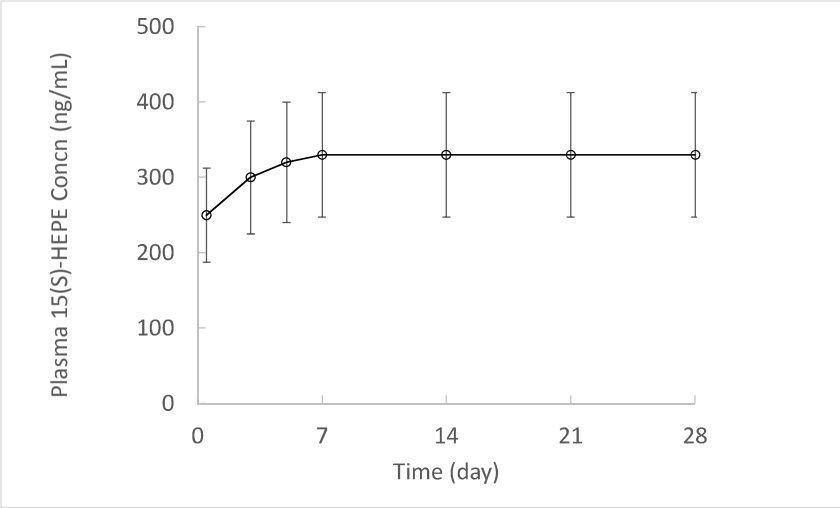



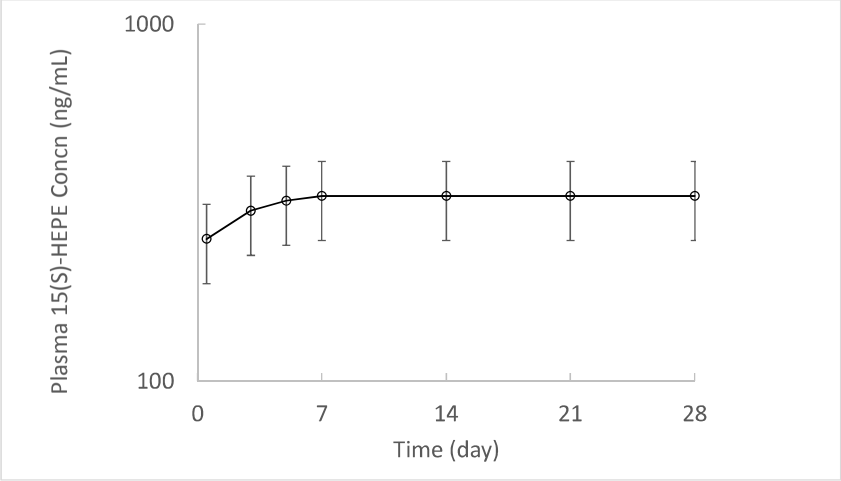

Note: Data below for plotting, not for printout

| Time (hr) | Day 0 | Day 7 |
|---|---|---|
| 0 | | |
| 0.5 | | |
| 1 | 17 | 29 |
| 2 | 900 | 1555 |
| 3 | 1800 | 3110 |
| 4 | 2400 | 4147 |
| 6 | 1100 | 1901 |
| 7 | 600 | 1037 |
| 8 | 390 | 674 |
| 10 | 350 | 605 |
| 12 | 330 | 570 |

**PK Mock Data Displays - FIGURES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**C** Free
**D** Total



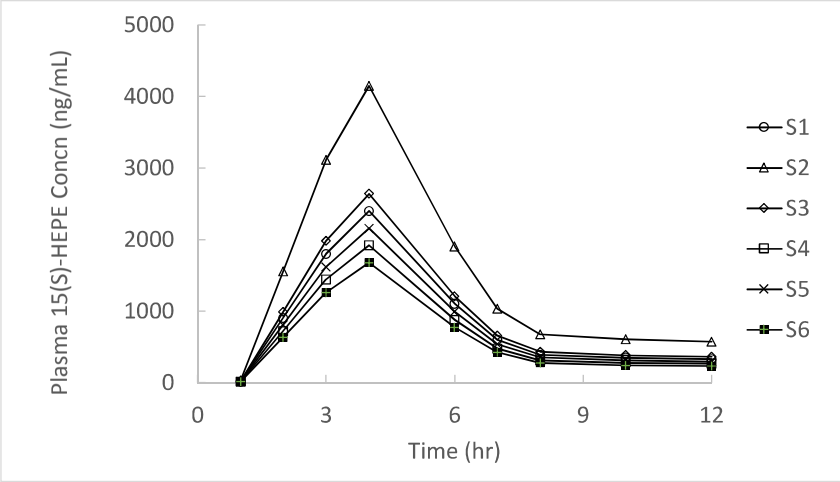



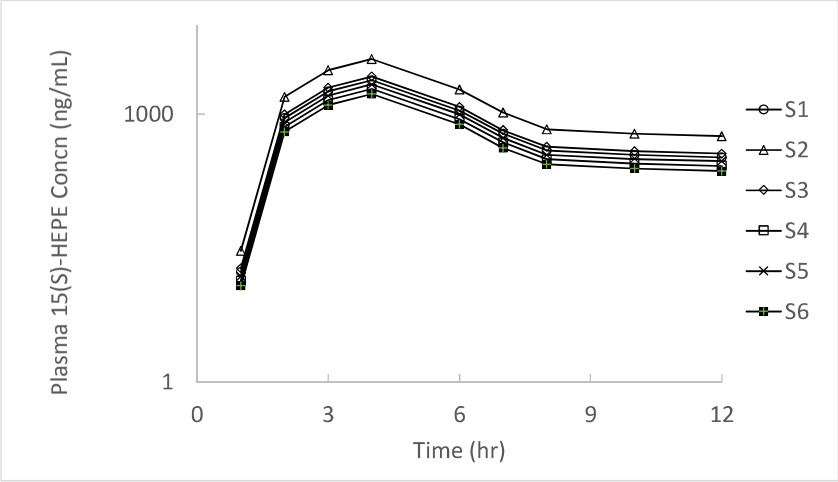

Note: Data below for plotting, not for printout

| Time (day) | Day 0 |
|---|---|
| 0 | |
| 0.5 | 250 |
| 3 | 300 |
| 5 | 320 |
| 7 | 330 |
| 14 | 330 |
| 21 | 330 |
| 28 | 330 |

**PK Mock Data Displays - FIGURES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**1** Free, Day 0
**2** Total, Day 0
**3** Free Day 7
**4** Total, Day 7



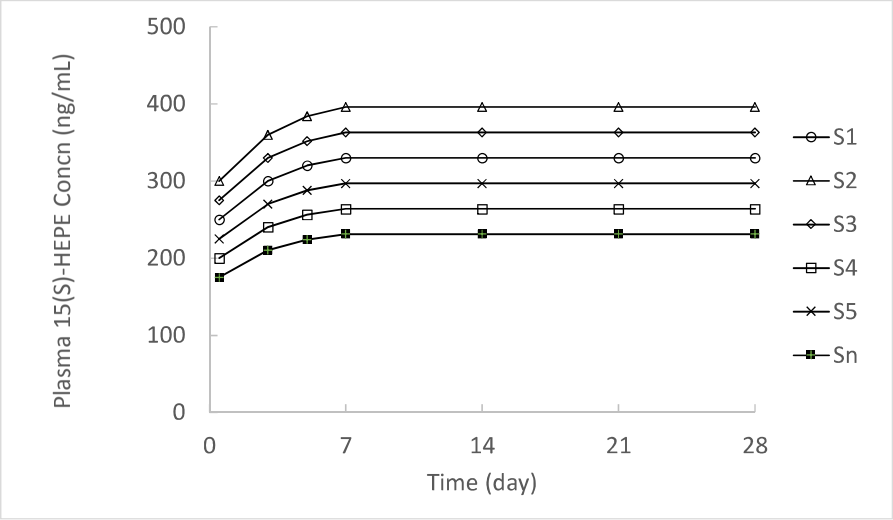



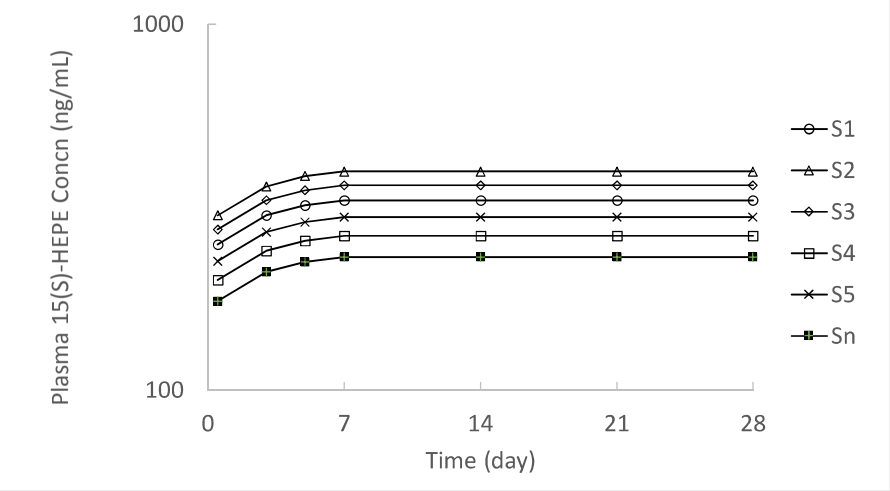

Note: Data below for plotting, not for printout

| Time (hr) | S1 | S2 | S3 | S4 | S5 | S6 |
|---|---|---|---|---|---|---|
| 0 | | | | | | |
| 0.5 | | | | | | |
| 1 | 17 | 29 | 19 | 14 | 15 | 12 |
| 2 | 900 | 1555 | 990 | 720 | 810 | 630 |
| 3 | 1800 | 3110 | 1980 | 1440 | 1620 | 1260 |
| 4 | 2400 | 4147 | 2640 | 1920 | 2160 | 1680 |
| 6 | 1100 | 1901 | 1210 | 880 | 990 | 770 |
| 7 | 600 | 1037 | 660 | 480 | 540 | 420 |
| 8 | 390 | 674 | 429 | 312 | 351 | 273 |
| 10 | 350 | 605 | 385 | 280 | 315 | 245 |
| 12 | 330 | 570 | 363 | 264 | 297 | 231 |

**PK Mock Data Displays - FIGURES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**5** Free
**6** Total



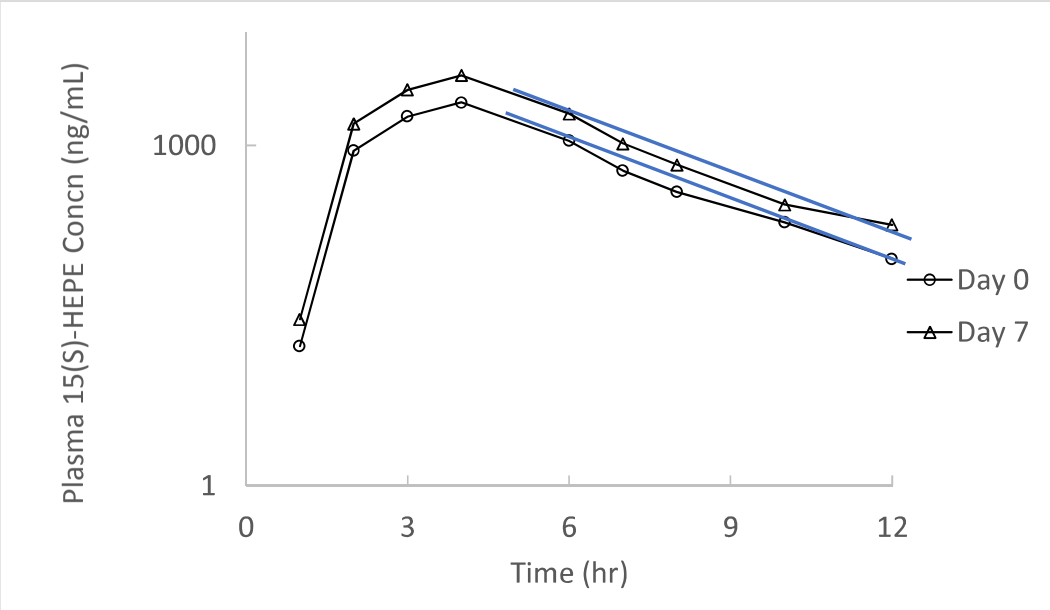




Note: Data below for plotting, not for printout

| Time (day) | S1 | S2 | S3 | S4 | S5 | Sn |
|---|---|---|---|---|---|---|
| 0 | | | | | | |
| 0.5 | 250 | 300 | 275 | 200 | 225 | 175 |
| 3 | 300 | 360 | 330 | 240 | 270 | 210 |
| 5 | 320 | 384 | 352 | 256 | 288 | 224 |
| 7 | 330 | 396 | 363 | 264 | 297 | 231 |
| 14 | 330 | 396 | 363 | 264 | 297 | 231 |
| 21 | 330 | 396 | 363 | 264 | 297 | 231 |
| 28 | 330 | 396 | 363 | 264 | 297 | 231 |

**PK Mock Data Displays - FIGURES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**1-6** Free
**7-12** Total



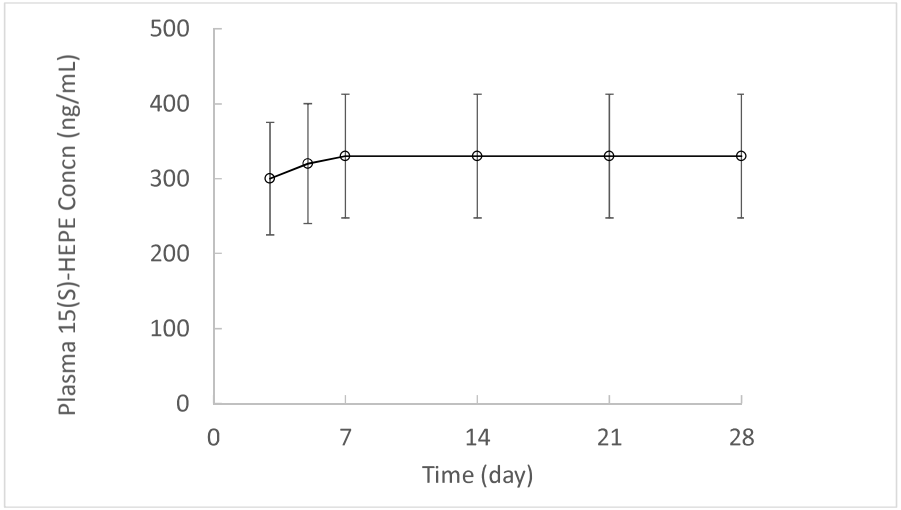

Note: Data below for plotting, not for prin

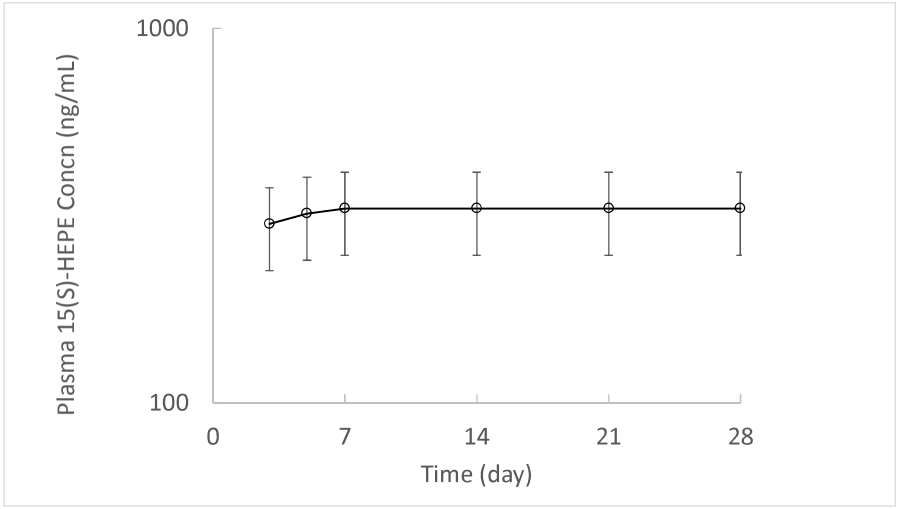
| Time (hr) | Day 0 | Day 7 |
|---|---|---|
| 0 | | |
| 0.5 | | |
| 1 | 17 | 29 |
| 2 | 900 | 1555 |
| 3 | 1800 | 3110 |
| 4 | 2400 | 4147 |
| 6 | 1100 | 1901 |
| 7 | 600 | 1037 |
| 8 | 390 | 674 |
| 10 | 210 | 300 |
| 12 | 100 | 200 |

tout

**PK Mock Data Displays - FIGURES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**x1** Free
**x2** Total



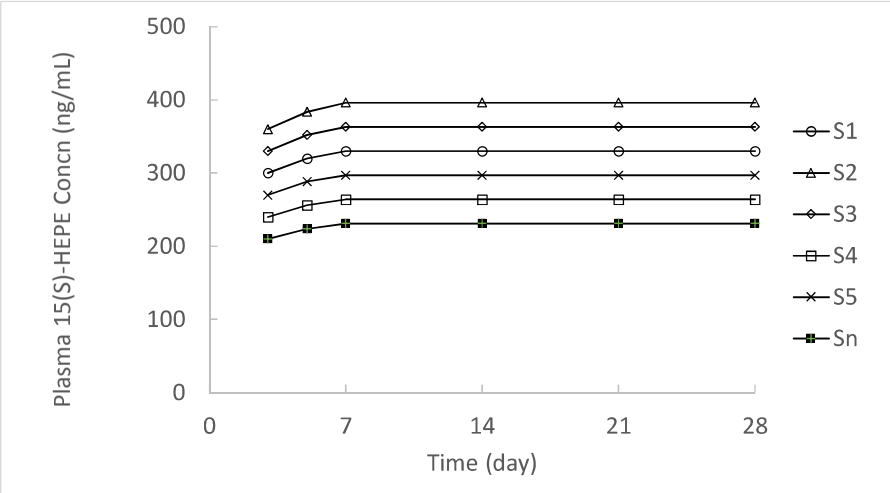



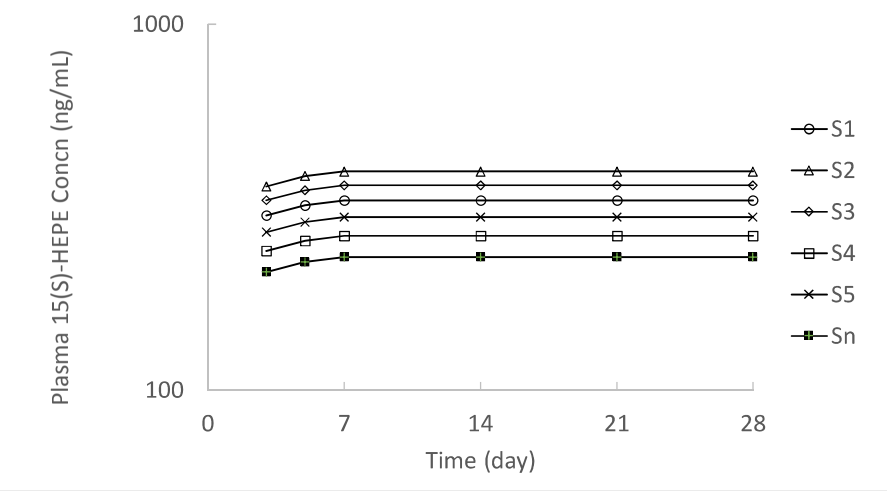

Note: Data below for plotting, not for printout

| Time (day) | Day 0 |
|---|---|
| 0 | |
| 3 | 300 |
| 5 | 320 |
| 7 | 330 |
| 14 | 330 |
| 21 | 330 |
| 28 | 330 |

**PK Mock Data Displays - FIGURES**
**Study DS102A-05-AH1**
**Pilot and Treatment Phases**
**PKPDS# Afm091318a**

**x3** Free
**x4** Total




Note: Data below for plotting, not for printout

| Time (hr) | S1 | S2 | S3 | S4 | S5 | Sn |
|---|---|---|---|---|---|---|
| 0 | | | | | | |
| 3 | 300 | 360 | 330 | 240 | 270 | 210 |
| 5 | 320 | 384 | 352 | 256 | 288 | 224 |
| 7 | 330 | 396 | 363 | 264 | 297 | 231 |
| 14 | 330 | 396 | 363 | 264 | 297 | 231 |
| 21 | 330 | 396 | 363 | 264 | 297 | 231 |
| 28 | 330 | 396 | 363 | 264 | 297 | 231 |

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Envelope Id: 48CDB6F02DB34F28BA09C054F65F86FE
Status: Completed
Subject: DS102A-05-AH1 (ANE18001): Statistical Analysis Plan for signature
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Signatures: 3
Certificate Pages: 5
Initials: 0
AutoNav: Enabled
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Diss Business Park
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elizabeth.gardener@synequanon.com
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| Moayed Hamza<br>M.Hamza@afimmune.com<br>Associate Medical Director<br>Security Level: Email, Account Authentication (Required) |  <br>Signature Adoption: Pre-selected Style<br>Signature ID:<br>F78A7A14-E5FE-4BA7-ACC2-D9A71DAFFFF1<br>Using IP Address: 86.47.150.97<br><br>With Signing Authentication via DocuSign password<br>With Signing Reasons (on each tab):<br>I approve this document | Sent: 25 January 2019 \| 19:02<br>Viewed: 28 January 2019 \| 12:06<br>Signed: 28 January 2019 \| 12:07 |
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|---|---|
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| Email: | Access to a valid email account |
| Screen Resolution: | 800 x 600 minimum |
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