STATISTICAL ANALYSIS PLAN

Protocol No.:	SHP626-201
Protocol Title:	A Phase 2 Double-Blind, Randomized, Placebo-controlled, Dose-finding Study to Evaluate the Safety, Tolerability and Efficacy of Volixibat Potassium, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi) in Adults with Nonalcoholic Steatohepatitis (NASH)
Drug:	Volixibat potassium (SHP626)
Sponsor:	Shire Development Inc. Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
Version No. and Date	Version 2.0, Date 26 July 2018

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Version 2.0	Updates for Final Analyses for abbreviated Clinical Study Report	Yi Chen	26Jul2018

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ABBREVIATIONS

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
BMI	Body mass index
DMC	Data monitoring committee
eCRF	Electronic case report form
ECG	Electrocardiogram
FAS	Full Analysis Set
FoTA	Final on Treatment Assessment
HbA1c	Hemoglobin A1c
HFF	Hepatic fat fraction
IA	Interim analysis
MedDRA	Medical Dictionary for Regulatory Activities
NAS	NAFLD activity score
NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic steatohepatitis
NASH CRN	NASH Clinical Research Network
OC	Observed cases
PBO	Placebo
PCI	potentially clinically important
PD	Pharmacodynamic
QTcB	QT Interval Corrected for Heart Rate using Bazett's Formula
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
T2DM	Type 2 Diabetes Mellitus
ULN	Upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the approved final study Protocol SHP626-201 Amendment 4 dated 25 Aug 2017. The plan provides a technical and detailed elaboration of the statistical analyses of safety, tolerability, and efficacy of volixibat in adults with nonalcoholic steatohepatitis (NASH). The specifications for tables, figures, and listings (TFLs) will be included in a separate document.

On Jun. 6th, 2018, the Data Monitoring Committee (DMC) for the SHP626-201 study recommended that the study be terminated after determining that no dose of volixibat was effective based on the predefined interim analysis criteria set for week-24 MRI PDFF and ALT. On Jun. 7th, 2018, the Shire Unblinded DMC Recommendation Review Team (Unblinded DMC RRT) reviewed the IA data and concurred with the DMC recommendation of SHP626-201 study termination.

As a result of the termination of the SHP626-201 study, an abbreviated clinical study report (CSR) will be written based on the results of the statistical analyses planned within this SAP. This SAP will not be used for any other analyses.

2. STUDY DESIGN

Refer to study Protocol SHP626-201 Amendment 4 dated 25 Aug 2017 for details on study design.

3. STUDY OBJECTIVES

Refer to study Protocol SHP626-201 Amendment 4 dated 25 Aug 2017 for details on study objectives.

4. SUBJECT POPULATION SETS

4.1 All Screened Set

The Screened Set will consist of all subjects who have signed an informed consent.

4.2 Randomized Set

The Randomized Set will consist of all subjects in the Screened Set who have been randomized into the study.

4.3 Safety Analysis Set

The Safety Analysis Set will consist of all subjects who take at least 1 dose of randomized IP, and have at least 1 post-baseline safety assessment (e.g., coming back for any visit, reporting of an AE or reporting the absence of AEs).

4.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the safety analysis set who have at least 1 post-baseline efficacy assessment (e.g., MRI, liver biopsy, serum liver-related biochemistry measurement).

4.5 Interim Analysis Set

The Interim Analysis Set (IAS) will consist of all subjects in the safety analysis set who have both baseline and scheduled Week 24 efficacy assessment (MRI and ALT biochemistry measurement) at the data cut time of the IA.

4.6 Pharmacodynamic (PD) Analysis Set

The PD Set will consist of all subjects who receive the IP and for whom at least 1 post first dose PD blood sample is collected.

5. SUBJECT DISPOSITION

The number of subjects included in each subject set (i.e., Screened, Safety, Randomized, FAS, Interim, and Pharmacodynamic) will be summarized by treatment group.

A listing of all screen failures (i.e., subjects who were screened but not randomized) will be presented along with reasons for screen fail and details of any AEs.

The number and percentage of subjects who completed and prematurely discontinued during the study will be presented for each treatment group and overall for safety analysis set subjects. Reasons for premature discontinuation from the study as recorded on the termination page of the eCRF will be summarized (number and percentage) by treatment group for the safety analysis set. All subjects who prematurely discontinued from the study will be listed by discontinuation reason for the randomized set.

The number of subjects enrolled, randomized and completed will be tabulated by site and country. In addition, the duration of enrollment, in days, will be summarized for each site, country, and overall. Duration of enrollment will be calculated as (last date of contact for any subject at that site - the first date of informed consent for any subject at that site + 1).

A listing for subject disposition and study analysis sets will be produced for all randomized analysis set.

6. PROTOCOL DEVIATIONS

A full list of protocol deviations will be compiled and reviewed by the clinical team to identify key versus non-key deviations before final database lock. For deviations at study entry, patients will be assessed against the inclusion and exclusion criteria of the protocol. For on-study deviations, compliance with the protocol will be examined using blinded review of the database with regard to prohibited therapies, timing and availability of planned assessments. All protocol deviation data will be listed.

7. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for the Safety Analysis Set. Baseline will be determined using the last observation collected before the first dose of investigational product.

The following demographic and baseline characteristics will be summarized in the tables: age, gender, ethnicity, race, weight, height, BMI, BMI category (<18.5, 18.5 - 25, 25 - 30 and >=30), waist circumference, hip circumference, waist to hip ratio, smoking history, baseline T2DM, NAS ={6, 7, 8} or NAS = {4, 5}, NAS (4, 5, 6, 7, 8), NAS, individual NAS components (steatosis, lobular inflammation, ballooning), SAF score, individual SAF components (steatosis, ballooning, lobular inflammation), fibrosis score, magnetic resonance imaging (MRI) hepatic proton density fat fraction (PDFF), expanded balloon score, portal inflammation, megamitochondria, acidophil bodies, fibrosis location if ≥ stage 2, steatosis zone, glycogenosis. Continuous variables will be summarized by descriptive statistics including number of subjects, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by the number of subjects in each category and the percentage of subjects out of the total in the corresponding analysis set.

Age will be calculated as the difference between date of birth and date of informed consent, rounded down to the last whole year. In the cases where there is a partial date of birth, if only day of the month is missing then the day will be imputed as 15, if both the day and month are missing then the day will be imputed as 1 and the month will be imputed as 7 (July).

Height and weight will be collected and used to calculate BMI using the following formula:

$$\text{BMI} = \frac{\text{Weight [Kg]}}{[\text{Height (m)} * \text{Height(m)}]}$$

BMI should be rounded to 1 decimal place for reporting purposes.

Waist to hip ratio is calculated as waist measurement divided by hip measurement (waist (cm) / hip (cm)). Waist to hip ratio should be rounded to 2 decimal places for reporting purposes.

A listing will be created to show all the demographic and baseline characteristics for each Safety Analysis Set subject.

Medical history will also be listed for the Safety Analysis Set.

Smoking history will be listed for the Safety Analysis Set.

8. EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

8.1 Exposure to Investigational product

Exposure to double-blind investigational product for the Safety Analysis Set will be summarized with descriptive statistics (n, mean, SD, minimum, median, and maximum) and presented by treatment group. Exposure and compliance to investigational product will be listed for the Safety Analysis Set. The following will be calculated for the investigational product:

- Treatment duration, which is calculated as the number of days from the date of first dose of double-blind investigational product taken to the date of the last dose of double-blind investigational product taken, inclusively. Investigators are allowed to interrupt the study treatment to allow adverse events to resolve, if necessary. Any drug interruption will be subtracted off the treatment duration above to get the final treatment duration. Treatment duration will be presented as the number of weeks in the summary tables.
- Total dose, which is calculated as (total dispensed – total returned) * xxmg.
- The average daily dose will be calculated as total dose from above / duration of study drug exposure in days.

8.2 Measurement of Treatment Compliance

Investigational product dosing compliance for a specified period is defined as the total number of capsules actually taken by a subject during that period divided by the number of capsules expected to be taken during the same period multiplied by 100. The total number of capsules actually taken is calculated by the total number of capsules dispensed minus the number of capsules returned. If a blister pack is not returned, the number of capsules returned for that blister pack will be imputed to zero. The number of capsules expected to be taken is calculated as the number of days that subject was in the particular period multiplied by the number of capsules to be taken per day during that period. The investigational treatment compliance over the entire study will be therefore calculated using the formula: $100 \times$ [(total

number of capsules dispensed) – (total number of capsules returned)]/ (total number of capsules planned to be taken per day × duration of study drug exposure in days). The investigational treatment compliance will be categorized as < 80, 80-120, and > 120% and the number and percentage of patients in the Safety Analysis Set will be presented by treatment group.

9. PRIOR AND CONCOMITANT MEDICATION AND THERAPIES

Version WHODRUG Jun_2016_DDE (Enhanced) of the World Health Organization (WHO) drug dictionary will be used to classify prior and concomitant medications and therapies by therapeutic class.

Prior medication/therapy is defined as any medication/therapy received within 30 days of the date of first dose of investigational product. Concomitant medication/therapy is defined as all treatment taken between the dates of the first dose of the IP and the end of the follow-up period, inclusive. Any medication with a start date after the end of follow-up period will not be considered a concomitant medication.

All prior, concomitant medications and therapies will be listed.

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10. SAFETY ANALYSES

The safety analysis will be performed by treatment using the safety analysis set. Safety variables include AEs, clinical laboratory variables, vital signs, and ECG variables. For each safety variable, the last value collected before the first dose of double-blind investigational product will be used as baseline for all analyses of that safety variable. A Final on-Treatment Assessment (FoTA) will be defined as the last valid assessment obtained after Baseline and whilst on investigational product and will be summarized in addition to all scheduled visits.

No inferential statistical analyses of safety endpoints will be performed.

10.1 Adverse Events

Adverse events will be coded using Version 19.0 of the Medical Dictionary for Regulatory Activities (MedDRA).

An AE (classified by preferred term) that occurs during the Double-blind Evaluation Phase or Follow-up Phase will be considered a TEAE if it has a start date on or after the first dose of double-blind investigational product and no later than the follow-up visit, or it has a start date before the date of the first dose of double-blind investigational product, but increases in severity on or after the date of the first dose of double-blind investigational product and no later than the follow-up visit. If more than 1 AE with the same preferred term is reported before the date of the first dose of double-blind investigational product, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the Double-blind Evaluation Phase or Follow-up Phase under the preferred term.

An overall summary of the number of subjects with TEAEs will be presented by treatment, including the number and percentage of subjects and absolute count of events for:

- Any TEAE,
- Any serious TEAE,
- Any TEAE related to investigational product in the opinion of the investigator,
- Any serious TEAE related to investigational product in the opinion of the investigator,

- Any TEAE leading to withdrawal of investigational product,
- Any severe TEAE,
- Any related severe TEAE
- Any TEAE leading to death

The number and percentage of subjects reporting TEAEs in each treatment group will be tabulated in the following ways:

- By System Organ Class (SOC) and preferred term;
- By Preferred term
- By SOC, preferred term, and maximum severity,
- Serious TEAEs by SOC and preferred term,
- TEAEs related to investigational product in the opinion of the investigator by SOC and preferred term
- TEAEs leading to withdrawal of investigational product (IP) by SOC and preferred term

If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product. The overall frequency will be considered for sorting purposes for the tables with SOC and PT.

In addition, for treatment emergent Diarrhea AEs the following will be summarized by treatment group: relative onset day, counts and percentages of events per subject, events treated with medication, outcome, drug withdrawn, duration of individual events (in days), duration of individual events treated with medication (in days), duration of individual events not treated with medication (in days), severity of diarrhea AEs, and worst severity of diarrhea AEs.

The incidence and prevalence of treatment emergent Diarrhea AEs will be summarized and plotted by study week for each treatment group. In addition a figure of all Diarrhea AEs over time will be presented displaying the severity of AEs, duration of AEs, and medication given.

All information about AEs collected on the eCRF will be listed alongside the treatment, preferred term, and SOC. For Serious AEs, deaths, AEs related to the investigational product, and TEAEs leading to study discontinuation, a separate listing will also be provided.

10.2 Clinical Laboratory Variables

Descriptive statistics for clinical laboratory values (in SI units) and changes from baseline at each post-baseline visit and at the FoTA visit for quantitative variables will be presented by treatment group for the clinical laboratory parameters in Table 1. A summary of liver enzyme elevations at each post-baseline visit, the FoTa visit, and overall post-baseline will be presented by treatment group for AST, ALT, and total bilirubin. The clinical laboratory test results will be listed for all subjects. The Evaluation of Drug Induced Serious Hepatotoxicity (eDISH) graph will also be provided for total bilirubin vs. ALT. Each point in the figure should represent a unique subject's peak serum ALT and peak serum total bilirubin (TB) values. Peak serum ALT is shown along the x-axis and peak TB is shown along the y-axis as x-fold upper limits of normal (ULN) on a log scale. The individual subject time course of ALT, AST, ALP, GGT and Total Bilirubin for Subjects with a Post-baseline ALT > 3xULN or Total Bilirubin > 2xULN will also be presented graphically (Figure 4.6.9.1). Subjects with Liver Enzyme Elevations: AST, ALT, ALP, GGT and Bilirubin will also be listed.

Table 1: Clinical Laboratory Evaluations

Biochemistry	Albumin (ALB)	
	Alkaline phosphatase (ALP)	Lactate dehydrogenase (LDH)
	Alanine aminotransferase (ALT; SGPT)	Protein
	Aspartate aminotransferase (AST; SGOT)	Magnesium (Mg)
	Blood urea nitrogen (BUN)	Potassium (K)
	C4	Uric acid

	Calcium (Ca)	Sodium (Na)
	Chloride (Cl)	Bicarbonate (CO2)
	Creatinine	Gamma glutamyl transferase (GGT)
	Creatine kinase	Glucose
	Phosphate (P)	Total and direct bilirubin
Coagulation	Activated partial thromboplastin time	International normalized ratio
	Prothrombin time	
Lipid Panel	Total Cholesterol	HDL Cholesterol
	LDL Cholesterol	Triglycerides
Endocrinology	Triodothyronine (T3)	Thyroid-stimulating hormone (TSH)
Hematology	Hemoglobin	Red blood cell (RBC)
	Hematocrit	White blood cell (WBC) count with differential
	Mean corpuscular hemoglobin (MCH)	Mean corpuscular volume (MCV)
	Platelets	Prothrombin time (PT)
	Activated partial thromboplastin time (aPTT)	International normalized ratio (INR)
Urinalysis	Appearance (clarity and color)	Microscopic examination of sediment
	Bilirubin	Nitrite
	Blood	pH
	Glucose	Protein
	Ketones	Specific gravity
	Leukocyte esterase	Oxalate
	Urobilinogen	
Other Lab Tests	Vitamin A	Vitamin D

	Vitamin E	HbA1c
	HOMA-IR	HOMA-%B

Clinical laboratory test values are potentially clinically important (PCI) if they meet either the low or high PCI criteria listed in Table 2. A supportive listing of subjects with post-baseline PCI values will be provided including the subject number, site, baseline, and post-baseline values.

Table 2: Criteria for Potentially Clinically Important Laboratory Tests

Test Name	PCI Criteria
Chemistry Panel	
Albumin	<3g/dl
Alkaline phosphatase (ALP)	>5 x ULN
Transaminase, SGOT, AST	>5 x ULN
Transaminase, SGPT, ALT	>5 x ULN
ALT or AST in combination with other events	(1) ALT or AST >3xULN and (Total Bilirubin >2xULN or INR >1.5) at same visit or (2) ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) at same visit
Blood Urea nitrogen (BUN)	>2.5 x ULN* (or alternatively H >30mg/dl**)
Calcium	<8mg/dl or >11.5mg/dl
Bicarbonate	<20 mEq/L or >30 mEq/L
Chloride	<90mEq/L or >110mEq/L
Creatinine, serum	>1.5 x ULN (or alternatively H >2mg/dl**)
Creatine Kinase	>1.5 x ULN
Gamma Glutamyl Transpeptidase (GGT)	>5 x ULN
Glucose, serum	<55mg/dl or >160mg/dl

Lactate dehydrogenase (LDH)	>3 x ULN*
Magnesium	<1.233mEq/L or >1.997mEq/L
Phosphorus, inorganic	<2.5mg/dl or >7.0mg/dl**
Potassium, serum/plasma	<3mEq/L (grade 3) or >5.5mEq/L
Sodium	<130mEq/L (grade 3) or >150mEq/L
Bilirubin, total	>2.0 x ULN
Direct bilirubin	>2.0 x ULN
Total protein, plasma or serum	<5g/dl* or >9g/dl*
Uric acid, serum / Urate	>8mg/dl
Endocrinology Panel	
Free T3/ Triodothyronine	< 1.4 pg/mL or > 7.5 pg/mL
Thyroid Stimulating Hormone (TSH) / Thyrotropin	<0.35 mIU/L or >6 mIU/L
Lipid Panel	
Total Cholesterol	<100mg/dL or ≥300mg/dl
HDL Cholesterol	≤40mg/dL
LDL Cholesterol	<50mg/dL or ≥150mg/dl
Triglycerides	>400mg/dL
Other Chemistry Tests	
Hemoglobin A1c	>0.09 Fraction of 1
Vitamin D, 25 Hydroxy	<12ng/mL

Retinol; Vitamin A	<1.0 x LLN
AlphaTocopherol	<1.0 x LLN
Coagulation	
Activated partial thromboplastin time	>1.3 x ULN
International normalized ratio	>1.3
Prothrombin time	>1.3 x ULN
Hematology	
Hemoglobin (HgB.)	<10g/dl
Hematocrit	<0.30 Fraction of 1 or >0.50 Fraction of 1
Mean Corpuscular Hemoglobin (MCH)~	<27pg or >32pg
Mean Corpuscular Volume (MCV)~	<70fL or >110 fL
Platelet count	$<75 \times 10^9$/L or $>500 \times 10^9$/L
Red Blood Cells (RBC) / Erythrocytes	male: $<2.5 \times 10^{12}$/L female: $<2.0 \times 10^{12}$/L
White Blood Cell Count (WBC) / Leukocytes	$<3 \times 10^9$/L or $>16 \times 10^9$/L
Neutrophils (absolute)	$<1.3 \times 10^9$/L
Neutrophils/Leukocytes	<0.15 Fraction of 1
Eosinophils/Leukocytes	<0.10 Fraction of 1

Basophils/Leukocytes	<0.15 Fraction of 1
Lymphocytes/Leukocytes	>0.80 Fraction of 1
Monocytes/Leukocytes	<0.40 Fraction of 1
Urinalysis	
Clarity	Any result other than clear
Color	Any results other than yellow
Bilirubin	Positive Value (excluding trace)
Blood / Occult Blood	Positive Value (excluding trace)
Glucose	Positive Value (excluding trace)
Ketones	Positive Value (excluding trace)
Leukocyte esterase	Positive Value (excluding trace)
Nitrite	Positive Value (excluding trace)
pH	<4.5 or >8
Protein	Positive Value (excluding trace)
Specific gravity	<1.005 or >1.025
Urobilinogen	>1 EU/dL
Microscopic Examination	
Red Blood Cells/Erythrocytes	≥ 5 /HPF
White Blood Cells/Leukocytes	≥ 5 /HPF
Bacteria	Any character value that is not “None” or “Rare” (or their equivalent)
Calcium oxalate crystals	Any present/positive (or equivalent)

*The NCI has not specified a value, Shire physicians have agreed on lab values provided.

** Values taken from the Reviewer Guidance, Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review, Table 7.1.7.3.2.1 pp 70-72. US DHHS FDA CDER, February 2005.

LLN: Lower limit of normal value provided by the laboratory
ULN: Upper limit of normal value provided by the laboratory

10.3 Vital Signs

Descriptive statistics for vital signs (temperature, sitting blood pressure (systolic blood pressure, diastolic blood pressure), pulse, respiratory rate, weight, waist circumference and waist:hip ratio) and their changes from baseline at each post-baseline visit and at the FoTA will be presented by treatment group. Vital signs data will be listed.

Vital sign values will be considered PCI if they meet the criteria listed in Table 3. A listing of subjects with post-baseline PCI values will be provided including the subject number, baseline, and post-baseline PCI values.

Table 3: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign Parameter	Flag	PCI Criteria	
		Observed Value	Change from Baseline
Systolic blood pressure (mmHg)	High	≥160	-
	Low	<90	-
Diastolic blood pressure (mmHg)	High	≥100	-
	Low	<60	-
Respiratory Rate (breaths per minute)	High	>25	-
	Low	<12	-
Pulse rate (beats per minute)	High	≥110	-
	Low	≤50	-
Weight (kg)	High	-	Increase of ≥5%
	Low	-	Decrease of ≥5%
Temperature (deg. C)	High	>39	-
	Low	<35	-

10.4 Electrocardiogram (ECG)

Descriptive statistics for ECG variables (heart rate, PR, RR, QRS, QTc and QT intervals) and their changes from baseline at each assessment time point will be presented by treatment

group. QTc interval will be calculated using both Bazett (QTcB=QT/(RR)1/2) and Fridericia (QTcF=QT/(RR)1/3) corrections; and if RR is not available, it will be replaced with 60/hr in the correction formula. A listing for 12-lead ECG results and interpretation by central reader.

Electrocardiogram variable values will be considered PCI if they meet or exceed the values listed in Table 4. A listing of all subjects with post-baseline PCI value will be provided including the subject number, baseline, and post-baseline PCI values.

Table 4: Criteria for Potentially Clinically Important ECG values

ECG Parameter	Unit	PCI Criteria	ECG Parameter
ECG Result	-	-	Abnormal and clinically significant from investigator
Heart Rate	beats/minute	≤50	≥110
PR Interval	msec	-	≥220
QT Interval	msec	-	≥480
QTc Interval	msec	-	≥460 and <480 ≥480 and <500 ≥500
QT/QTc increase from baseline	Msec	-	≥30 and <60 ≥60
QRS Interval	Msec	-	≥120

10.5 Other Safety Variables

10.5.1 Bristol Stool Chart

The Bristol Stool Chart (BSC) is a medical aid designed to classify the form of human feces into seven categories, where 1 is the hardest and 7 is the softest. Types 3 and 4 would be normal and types at either end of the scale would be severe. Stools will be assessed by the bowel movement consistency of the softess stool within the last 24 hours prior to the clinic visit. BSC responses on the rating scale of stool hardness (Type 1 to Type 7) will be listed by time point and treatment group. Summaries of stool hardness by time point and treatment group will be provided.

Stool frequency will be assessed by the number of bowel movements within the last 24 hours prior to the clinic visit. Summary statistics (number of observations, mean, SD, median, maximum, and minimum) will also be presented by treatment group for frequency of bowel movements by day. The stool frequency would be PCI if it is ≥6 BM/day.

11. CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

11.1 Pharmacokinetics Population and Pharmacodynamics Population

Pharmacokinetic data was not collected in this study. For pharmacodynamics population, see section 4.6.

11.2 Pharmacokinetic Methods

N/A

11.3 Statistical Analysis of Pharmacokinetic Data

N/A

11.4 Pharmacodynamic Methods

BA synthesis will be assessed via alpha-hydroxy-4-cholesten-3-one [C4] concentrations.

11.5 Statistical Analysis of Pharmacodynamic Data

C4 concentration data will be listed.

12. OTHER ANALYSES

12.1 Health-related Quality of Life Analyses

All Health-related Quality of Life data will be listed for the full analysis set.

13. COMPUTER METHODS

Data analyses will be performed by ICON. Statistical analyses will be performed using Version 9.3 (or newer) of SAS® on a suitably qualified environment.

14. DATA HANDLING CONVENTIONS

14.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, SD, minimum, maximum. The minimum and maximum values will be presented to the same number of decimal places as the raw data. The mean and median will be presented to one more decimal place than the raw data. The SD will be presented to two more decimal places than the raw data.

Categorical data and count variables will be summarized using n and percentages based on the number of non-missing values. Percentages will be presented to one decimal place. The number of missing values will be presented as a separate category with no percentage, but only if 1 or more patients are missing data for the summary. Otherwise, all categories will be presented (even if no patients are counted in the category). Counts of zero in any category will be presented without a percentage.

14.2 Derived Efficacy Endpoints

NAS, MRI-PDFF, HOMA-IR, and SAF will be derived in the dataset according to the rules in Appendix 2 of the protocol. If any of the individual components are missing, then the corresponding NAS, SAF, MRI and HOMA –IR will be set to missing.

MRI hepatic PDFF will be derived based on images from multi-echo (ME) and double double echo (DDE) sequences.

The MRI hepatic PDFF endpoint will be derived in four ways:
1) The first analyzable ME result will be used at a visit. If the ME is not analyzable the DDE will be used at a visit. ME results are selected preferentially. If neither ME nor DDE is analyzable, a repeat will be requested and if repeat is requested then the result to use is based on the ME preferentially then the DDE on this repeated imaging. It is possible for the baseline to come from ME and week 24 to come from DDE and vice versa. This will be the primary definition of the MRI hepatic PDFF endpoint as suggested by the expert radiologist.

2) Use MRI hepatic PDFF only based on ME images. Only those subjects with both an analyzable ME at baseline and at week 24 will be included in change from baseline analyses. 3) Use MRI hepatic PDFF only based on DDE images. Only those subjects with both an analyzable DDE at baseline and at week 24 and week 24 will be included in change from baseline analyses. 4) If ME is available at both baseline and week 24 then the MRI hepatic PDFF endpoint should be based on ME images. Otherwise, if DDE is available at both baseline and week 24 then the MRI hepatic PDFF endpoint should be based on DDE images.

14.3 Association of Early Termination Assessments to Scheduled Visits

For purposes of reporting early termination assessments during the study, each early termination visit will be mapped to a visit according to the visits window in Appendix 1. This rule applies to both efficacy variables (e.g., ALT) and safety variables (e.g., vital signs) that are analyzed and/or summarized by visit.

14.4 Repeated or Unscheduled Assessments of Safety Parameters

Unscheduled visits will be mapped to a visit according to the visits window in Appendix 1.

If a subject has repeated assessments before the start of investigational product, then the results from the final assessment made prior to the start of investigational product will be used as baseline.

If a subject has repeated assessments after the start of investigational product within a visit window, only the scheduled visit will be used for efficacy analyses. For safety analyses, the results from scheduled visit will be used first, if no scheduled visit, the record from the visit closest to target date will be used. If there are multiple records with the same distance to the target date, the latest record will be used.

If the final on-treatment safety assessments are repeated or unscheduled, the last post-baseline assessment will be used as the final on-treatment assessment for generating descriptive statistics.

However, all post-baseline assessments will be used for PCI value determination and all assessments will be presented in the data listings.

14.5 Missing Date of Investigational Product

When the date of the last dose of investigational product is missing for a subject in the Safety Analysis Set, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last visit date when investigational product was returned will be used in the calculation of treatment duration.

14.6 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, including rescue medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed. When the start date and the stop date are both incomplete for a subject, impute the start date first.

14.6.1 Incomplete Start Date

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced.

- If the year of the incomplete start date is the same as the year of the date of the first dose of investigational product, then the day and month of the date of the first dose of investigational product will be assigned to the missing fields
- If the year of the incomplete start date is before the year of the date of the first dose of investigational product, then December 31 will be assigned to the missing fields
- If the year of the incomplete start date is after the year of the date of the first dose of investigational product, then 01 January will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of investigational product, then the day of the date of the first dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the first dose of investigational product or if both years are the same but the month is before the month of the date of the first dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the date of the first dose of investigational product or if both years are the same but the month is after the month of the date of the first dose of investigational product, then the first day of the month will be assigned to the missing day.

14.6.2 Incomplete Stop Date

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of investigational product is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced.
- If the year of the incomplete stop date is the same as the year as of the date of the last dose of investigational product, then the day and month of the date of the last dose of investigational product will be assigned to the missing fields
- If the year of the incomplete stop date is before the year of the date of the last dose of investigational product, then 31 December will be assigned to the missing fields
- If the year of the incomplete stop date is after the year of the date of the last dose of investigational product, then 01 January will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of investigational product, then the day of the date of the last dose of investigational product will be assigned to the missing day
- If either the year is before the year of the date of the last dose of investigational product or if both years are the same but the month is before the month of the date of the last dose of investigational product, then the last day of the month will be assigned to the missing day
- If either the year is after the year of the last dose of investigational product or if both years are the same but the month is after the month of the date of the last dose of

investigational product, then the first day of the month will be assigned to the missing day.

14.7 Missing Date Information for Adverse Events

For AEs, the default is to only impute incomplete (i.e., partially missing) start dates. Incomplete stop dates may also be imputed when calculation of the duration of an AE is required per the protocol. If imputation of an incomplete stop date is required, and both the start date and the stop date are incomplete for a subject, impute the start date first.

14.7.1 Incomplete Start Date

Follow same rules as in Section 14.6.1.

14.7.2 Incomplete Stop Date

Follow the same rules as in 14.6.2.

14.8 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

14.9 Missing Relationship to Investigation Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to double-blind investigational product will be used for incidence summaries, while the actual values will be presented in data listings.

14.10 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a statistical analysis due to, for example, that a character string is reported for a numerical variable. The appropriately determined coded value will be used in the statistical analysis. However, the actual values as reported in the database will be presented in data listings.

15. APPENDIX

Appendix 1: Classification of Visits Window

Timing of assessment (days relative to Treatment a)	Visit	Visit Name to display for Analysis
<=-1 Day	Screening	Visit 1 (Screening)
Visit 2 (Week 0 [Day 1])	Baseline	Visit 2 (Baseline)
Week 2, Day 14 (2-22 Days)	Visit 3	Visit 3 (Week 2)
Week 4, Day 28 (23-43 Days)	Visit 4	Visit 4 (Week 4)
Week 8, Day 56 (44-71 Days)	Visit 5	Visit 5 (Week 8)
Week 12, Day 84 (72-127 Days)	Visit 6	Visit 6 (Week 12)
Week 24, Day 168 (128-211 Days)	Visit 7	Visit 7 (Week 24)
Week 36, Day 252 (212-295 Days)	Visit 8	Visit 8 (Week 36)
Week 48, Day 336 (296 Days-End of Study)	Visit 9- End of Treatment	Visit 9 (Week 48)
Week 52, 4 weeks after completion of dosing (>End of Study)	Visit 10-Follow-up	Visit 10 (Week 52)

* For early termination patients, MRI and liver biopsy visits happened after early termination date will be mapped to same visit as the early termination visit, even though the visit date is later than End of Study date.

16. REFERENCES

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