Statistical Analysis Plan

An open-label, randomized, 3-arm, parallel group, positive- and negative-arm-controlled study to evaluate the mineralocorticoid receptor antagonism effect of vamorolone in healthy subjects

Sponsor: Santhera Pharmaceuticals (Switzerland) AG

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Version History

SAP Final Version	Date	Change	Rationale
1.0	03-JUL-2024	Not Applicable	Not Applicable
2.0	17-JUL-2024	Handling of Na and K values <LLOQ	In cases where concentrations of Na and/or K is <LLOQ, the concentrations will be set to ½ LLOQ for further calculation of the ratios.

1. ABBREVIATIONS

Abbreviations and definitions of PK parameters are provided in Section 12.1.

AE	Adverse event
BMI	Body mass index
CSR	Clinical study report
CV	Coefficient of variation
DRM	Data Review Meeting
ECG	Electrocardiogram
ICH	International Council for Harmonisation
K	Potassium
LLOQ	Lower limit of quantification
MCAR	Missing completely at random
MedDRA	Medical dictionary for regulatory activities
MRA	Mineralocorticoid receptor antagonist
N, n	Number
Na	Sodium
NCA	Non-compartmental analysis
PD	Pharmacodynamics
PK	Pharmacokinetics
QRS	Part of electrocardiographic wave representing ventricular depolarization
QT	QT interval uncorrected
QTc	QT interval corrected
QTcF	QT interval corrected for ventricular rate calculated according to the formula of Fridericia
Rel	Relative
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard deviation
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TLF	Tables, listings, figures

TOC	Table of Contents
WHO	World Health Organization

2. INTRODUCTION

The objective of this statistical analysis plan (SAP) is to specify the statistical analysis in more detail than stated in the protocol for the trial. The statistical analysis plan does not change the analysis described in the protocol, but it should be precise enough to serve as a guideline for statistical programming and creation of tables.

This SAP was developed with reference to the valid protocol (final version 2.0, dated 18-APR-2024). Supplementary text to the protocol gives a full specification of analyses and presentation. If applicable, deviations from the planned methods stated in the protocol are summarized in Section 17. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in an amendment to this SAP or in the clinical study report (CSR). Any substantial deviations from this SAP will be agreed upon between the Sponsor and Nuvisan and discussed in the CSR.

3. STUDY OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**
Primary	
• To investigate the mineralocorticoid receptor antagonist (MRA) effect of vamorolone by measuring the anti-aldosterone activity using mineralocorticoid challenge with fludrocortisone in healthy subjects	• Determination of the ratio of sodium (Na) to potassium (K) (Na/K) in urine
Secondary	
• To investigate the safety and tolerability of vamorolone combined with fludrocortisone challenge	• Treatment emergent adverse events (TEAE), laboratory assessments, vital signs and electrocardiogram (ECG) evaluation
• To evaluate the pharmacokinetic (PK) of a single dose of vamorolone (20 mg/kg) combined with fludrocortisone challenge (Day 2)	• Plasma PK parameters $AUC_{0\text{-tlast}}$, $AUC_{0\text{-inf}}$ and C_{max}
• To evaluate the PK of a single dose of eplerenone (200 mg) combined with fludrocortisone challenge (Day 2)	• Plasma PK parameters $AUC_{0\text{-tlast}}$, $AUC_{0\text{-inf}}$ and C_{max}
Tertiary/Exploratory	
Not applicable.	

4. DESIGN OF THE STUDY

This study will be conducted in a single-center, randomized, open-label, 3-arm, parallel group, positive- and negative-controlled design. The purpose of this study is to investigate the antagonistic effect of vamorolone on the MR following mineralocorticoid challenge by fludrocortisone,

compared to eplerenone as a positive control, and an observation arm with no study treatment administered as a negative control. Furthermore, the safety and tolerability of vamorolone combined with fludrocortisone challenge will be assessed, and the PK of a single dose of vamorolone and a single dose of eplerenone, combined with fludrocortisone challenge, will be evaluated.

30 healthy male subjects (18 to 55 years, inclusive) will be randomized to one of the 3 arms:
- Arm 1 (experimental arm): Vamorolone
- Arm 2 (positive control arm): Eplerenone
- Arm 3 (negative control arm): No treatment

Dropouts may be replaced if the number of evaluable subjects completing the study becomes or is expected to become less than 24 subjects in total, i.e., less than 8 subjects in each study arm.

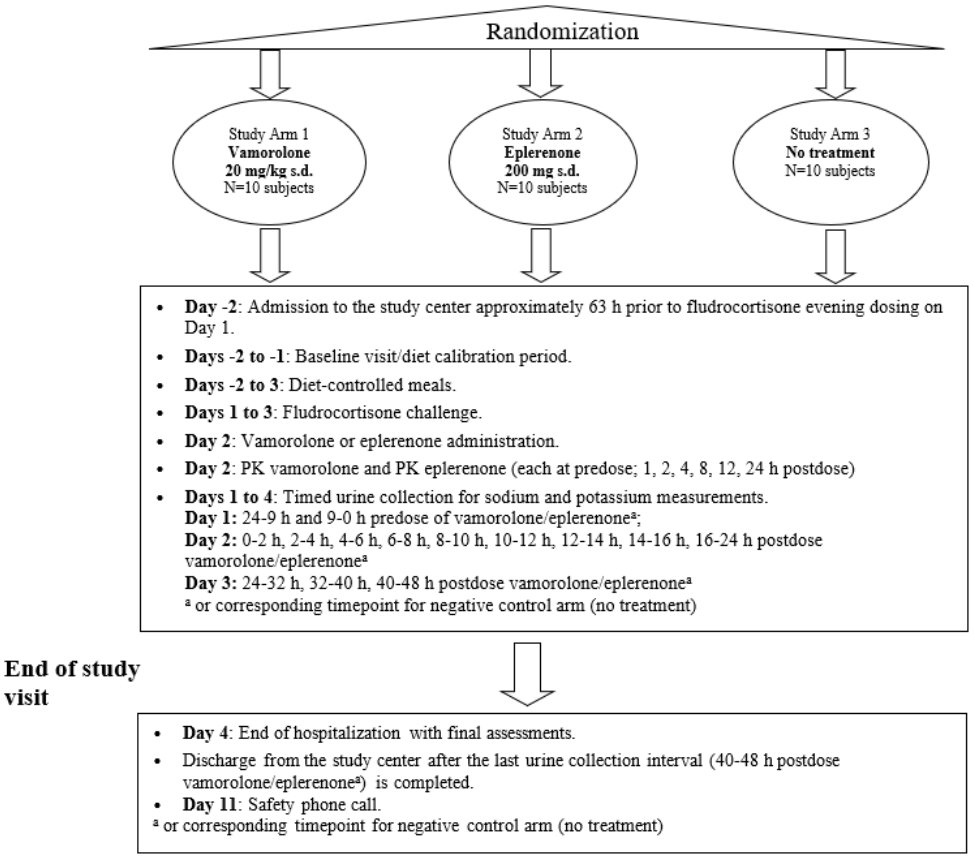
The maximum total duration for a subject in the study will be approximately 32 days, from screening until the follow-up safety phone call. Subjects will be screened for eligibility within 19 days of admission. Subjects will be admitted to the study site on Day -2 and will remain inpatient at the study site under medical supervision until discharge on Day 4. The treatment duration will be 3 days and subjects will receive the study treatments as follows.

Fludrocortisone challenge on Days 1 to 3 (for all subjects):
Day 1:
Fludrocortisone 1 mg at 9 h predose vamorolone/eplerenone administration/corresponding timepoint for negative control arm.
Day 2:
- Fludrocortisone 0.5 mg at the same time of vamorolone/eplerenone administration in the morning (0 h)/corresponding timepoint for negative control arm.
- Fludrocortisone 0.1 mg at 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, and 14 h vamorolone/eplerenone postdose administration/corresponding timepoint for negative control arm.
- Fludrocortisone 0.5 mg at 16 h vamorolone/eplerenone postdose administration/corresponding timepoint for negative control arm.

Day 3:
Fludrocortisone 0.1 mg at 24 h vamorolone/eplerenone postdose administration on Day 2/ corresponding timepoint for negative control arm.

Day 2: drug administration period (vamorolone or eplerenone or no treatment)
- 10 subjects randomized to study arm 1 will receive a single oral dose of 20 mg/kg vamorolone
- 10 subjects randomized to study arm 2 will receive a single oral dose of 200 mg eplerenone
- 10 subjects randomized to study arm 3 will receive no treatment

Subjects will be served standardized, diet-controlled meals from Day -2 to Day 2, i.e., containing similar quantities of sodium and potassium. The follow-up visit is planned 2 days after the last dose of study treatment, on Day 4. A follow-up safety phone call is planned on Day 11. Early discontinuation assessments will be conducted at an early discontinuation visit for subjects who have withdrawn prematurely.



5. STATISTICAL HYPOTHESIS

No formal statistical hypotheses have been defined for this exploratory study (protocol section 9.1).

6. SAMPLE SIZE AND POWER ESTIMATION

30 subjects will be randomly assigned to study treatment such that 24 evaluable subjects complete the study, i.e., 8 subjects in each study arm. The estimated sample size was based on sample sizes from previous studies (protocol section 9.5).

7. ANALYSIS SETS AND PROTOCOL DEVIATIONS

7.1. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Full Set	All subjects enrolled in the study.
Safety	All subjects assigned (randomized) to study treatment and who receive at least 1 dose of study treatment. Subjects will be analyzed according to the treatment they received. This population will be used for safety analyses, if not stated otherwise.

Pharmacokinetics	This set is a subset of the safety set and includes all subjects who complete the study without any findings/events likely affecting PK. This population will be used for PK analyses, if not stated otherwise. *Subjects receiving study intervention arm 3 should be excluded from the Pharmacokinetics Set.*
Pharmacodynamics	This set is a subset of the safety set and includes all subjects who complete the study without any findings/events likely affecting PD. This population will be used for PD analyses, if not stated otherwise.

7.2. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design, or procedures defined in the protocol. Protocol deviations will be identified prior to database lock.

Important protocol deviations are a subset of protocol deviations that may significantly affect the completeness, accuracy and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

Important protocol deviations will be listed.

A protocol deviation may also be declared as finding/event that led to an exclusion of data or complete subjects from an analysis set.

Protocol deviations as well as findings/events leading to the exclusion from analysis sets will be pre-specified in a deviation manual and collected in a quality issue log on an ongoing basis. This quality issue log will finally be discussed and agreed on in a Data Review Meeting (DRM) prior to database lock and prior to availability of bioanalytical data to those who decide on the allocation of subjects to analysis sets.

The listings that are compiled by the biostatistics department for the DRM are marked with an asterisk ('*') in Section 19.2.

8. GENERAL CONSIDERATIONS

8.1. General Rules

Generally, all data entered into the database will be listed by subject and summarized descriptively.

If not stated otherwise, descriptive statistics for qualitative data include number of cases including percentages. The percentages will be calculated based on the number of subjects in the population for overall summaries and on the number of subjects in the population receiving the respective study treatment for summaries by study treatment (denoted as "N"). Descriptive statistics for quantitative data include, if not stated otherwise: number of evaluable cases/measurements (denoted as "n"), mean, standard deviation (SD), coefficient of variation (CV, in %), minimum, median, maximum, interquartile range (Q1; Q3). For PK concentrations and PK parameters related to concentrations, geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms), and geometric CV (in %) will also be derived. For PK concentration only, geometric "n" will also be derived.

In general, for repeated measurements after the first administration of study treatment (i.e., administration of fludrocortisone on Day 1), the first one will be used in the statistical calculations for presentation in the tables of descriptive statistics (unless the scheduled measurement was considered unreliable, e.g., due to technical reasons, and needed to be replaced by an unscheduled repeat measurement). For repeated measurements before first administration of study treatment, the last one will be used in the statistical analysis. Although only one value per visit is selected for analysis, all data are presented in the data listings.

Data listings will include all subjects, i.e. evaluable and not evaluable, and will be sorted by subject and time point for each study treatment arm. Subjects will be identified by the randomization number, where applicable. Only demographic and population listing will show the screening and randomization number.

8.2. Imputation of Missing Data

All data will be used to their largest possible extent. Number of missing observations is expected to be very low in that Phase I healthy volunteer study. Any missing observation will be assumed to be missing completely at random (MCAR). Missing data will not be replaced or imputed in any way, if not stated otherwise in the SAP.

8.3. Definition of Relative Days and Duration

For the calculation of relative days, the following definitions will be applied:

1. Day 1 is the day of first administration of study treatment. Each study day before and thereafter is defined relative to Day 1.
2. Relative (Rel.) Day of events on or after Day 1 as defined above = start date of the event – date of first administration of study treatment + 1
3. Rel. Day of events before Day 1 = start date of the event – date of first administration

The following definitions and calculations of duration, as applicable, will be applied:

1. Duration of event (in days hh:mm) = end date and time – start date and time of the event
2. Days hh:mm from dosing (onset post administration) = start date and time of the event – date and time of last administration of study treatment (calculated for each treatment)
3. Study treatment duration (in days) = date of last administration of study treatment – date of first administration of study treatment + 1
4. If start time of an event is missing, then it will be imputed by “00:00”, if end time of an event is missing then it will be imputed by “23:59”

9. SOFTWARE

Software to perform statistical analyses will be SAS® version 9.4 or higher, if not stated otherwise. The non-compartmental PK analysis of the data will be accomplished by using Phoenix WinNonlin® version 8.3 or higher, if not stated otherwise. If a PK parameter is not automatically calculated within WinNonlin®, then the concentration data itself or WinNonlin® derived parameters will be used to determine these subsequent PK parameters and will be calculated within SAS®.

10. STUDY SUBJECTS AND DEMOGRAPHIC CHARACTERISTICS

The number and percentage of subjects who are screened, randomized (N), treated with study treatment, completed or discontinued study as well as the reason for study termination will be summarized by study treatment arm and overall in a disposition frequency table for all subjects.

Re-screened subjects will be annotated accordingly in the listings and counted as only one subject in the disposition table.

A frequency table of number and percentage of subjects in the Safety Set, Pharmacokinetics Set, and Pharmacodynamics Set will be provided by study treatment arm and overall for all randomized subjects (N).

Demographic variables and baseline physical characteristics will be listed by subject and summarized by study treatment arm and in total for the Safety Analysis Set (and all other analysis sets, if different) using descriptive statistics for continuous variables (age, height, weight, body mass index (BMI)) and using frequencies for categorical variables (sex, ethnicity, race).

Violation of inclusion and exclusion criteria will be listed.

Lifestyle restrictions such as diet-controlled meal and fluid consumption (i.e., drink of non-carbonated water) will be listed by subject.

Any prior medication, concomitant medication and procedures will be encoded with World Health Organization (WHO) Drug Global Dictionary and will be listed by subject. Any medication taken at or after the time of first study treatment, regardless of whether it had started prior to the study or not, is to be recorded as concomitant medication. Prior medications are defined as any medication taken which had been stopped prior to the first administration of study treatment.

Medical history will be listed by subject.

11. EFFICACY ANALYSES

Not applicable.

12. PHARMACOKINETIC ANALYSES

12.1. Pharmacokinetic Parameters

PK parameters will be calculated for subjects in the Pharmacokinetics set. The PK parameters that will be calculated for each subject in study treatment arm 1 (vamorolone dosing) and study treatment arm 2 (eplerenone dosing) by non-compartmental analysis (NCA) for levels of vamorolone and eplerenone in plasma are listed below. They will be calculated relative to treatment administration on Day 2.

$AUC_{0\text{-}tlast}$ = The area under the concentration-time curve (AUC) from time zero (= dosing time) to the time of the last quantifiable concentration (t_{last}), calculated using linear trapezoidal rule.

$AUC_{0\text{-}inf}$ = The AUC from time zero (dosing time) extrapolated to infinity estimated using the log-linear regression for λ_z determination (see below):
$AUC_{0\text{-}inf} = AUC_{0\text{-}tlast} + C_{last}/\lambda_z$.

(C_{last} = observed concentration at the last sampling time (t_{last}) at which the concentration is at or above the lower limit of quantification)

C_{max} = Maximum observed concentration.

$t_{½}$ = Apparent terminal half-life, calculated as $(\ln 2)/\lambda_z$

t_{max} = The time to reach the maximum observed concentration collected during a dosing interval (unless otherwise defined, take the 1st occurrence in case of multiple/ identical C_{max} values).

λ_z = Terminal first order (elimination) rate constant, determined from the terminal slope of the concentration-time curve using log-linear regression on terminal data points

Phoenix WinNonlin® method linear trapezoidal linear/log interpolation will be used for calculation of AUC.

The pre-dose plasma sample always will be considered as if it had been taken simultaneously with the drug administration. If there should have been any deviations in post-dose sampling, the actual sampling times relative to drug administration will be used unless stated otherwise. Missing data will not be replaced or imputed in any way. Scheduled time will be used for calculation of PK parameters in case of missing sampling times. Plasma concentrations below the lower limit of quantification (LLOQ) will be treated as zero.

AUC will be regarded as unreliable if more than two consecutive concentrations are missing or if the concentrations were quantifiable and/or non-missing for fewer than 2/3 of the time points. In this case all derived parameters will be calculated but also considered as unreliable.

C_{max} and t_{max} will be regarded as unreliable if the maximum was observed preceding or following a sample with missing data. In case of multiple peaks, C_{max} and t_{max} refer to the highest measured concentration even if there should be earlier peaks. In case of two or more samples with the same concentration (as supplied by the analyst), t_{max} refers to the earlier of these.

Log-linear regressions for determination of λ_z should exclude t_{max} and will be performed using at least 3 data points of the terminal elimination phase. Concentrations < LLOQ after the last quantifiable data point > LLOQ should not be used in the regression analysis.

λ_z will not be calculated, if the terminal elimination phase is not apparent.

λ_z will be calculated but considered as unreliable if the R^2 value is less than 0.8. In this case, all derived parameters ($AUC_{0\text{-}inf}$, $t_{½}$) will still be calculated but also considered as unreliable.

The value of $AUC_{0\text{-}inf}$ will also be considered unreliable if the terminal area beyond the last quantified sample is greater than 20% of the total $AUC_{0\text{-}inf}$. In this case all derived parameters will be calculated but also considered as unreliable.

Unreliable parameters will be listed and flagged accordingly and set to missing for calculation of descriptive statistics and statistical analysis. If a PK parameter is unreliable for more than 20% of the subjects, this parameter will additionally be evaluated as sensitivity including the unreliable cases.

12.2. Presentation of Data

The results of subject plasma concentration samples measured will be listed separately for each study treatment arm (vamorolone and eplerenone) and tables will be prepared showing descriptive statistics as described in Section 8.1 for concentrations at each sampling time by study treatment arm. Samples with concentrations below LLOQ will be identified in listings (i.e. <LLOQ). Individual concentration values below LLOQ will be set to zero for the calculation of summary statistics and for plotting.

Similar listings and tables will also be prepared for PK parameters in plasma. Tables will show descriptive statistics as described in Section 8.1, except for t_{max}, only minimum, median, and maximum will be reported.

$\%AUC_{extrap}$ will be listed only. The auxiliary parameters R^2, the starting and end time (lower and upper limit), and number of points considered in calculation of λ_z will also be listed only.

For each study treatment arm (vamorolone and eplerenone) and each subject with plasma concentration data, individual plasma concentration-time profiles will be plotted on a linear as well as on a log-linear scale. Similar plots will also be generated for the mean plasma concentration-time profiles by study treatment arm (incl. figures showing the arithmetic mean course without standard deviation on a linear as well as on a log-linear scale and a figure showing the arithmetic mean course with standard deviation on a linear scale). The actual sampling times for individual plots and the scheduled sampling times for mean plots will be used. The same rules of handling concentrations below LLOQ as defined above will be applied for the plots.

12.3. Analysis of Pharmacokinetic Parameters

PK parameters will be summarized descriptively by study treatment arm (vamorolone and eplerenone) as mentioned above in Section 12.2.

13. PHARMACODYNAMIC ANALYSES

13.1. Pharmacodynamic Parameters

Pharmacodynamic (PD) parameters will be calculated for subjects in the Pharmacodynamics set.

For urine collection the actual starting time of the first collection interval (pre-dose voiding) will precede drug administration and similarly the collection interval scheduled to end after one dosing interval actually will end (subject being sent to toilet) slightly earlier than scheduled. These effects are considered to counterbalance and there will be no attempts to correct excreted amounts.

Urine samples will be collected for measurement of sodium (Na) and potassium (K) in each study treatment arm (i.e., vamorolone, eplerenone, and negative control arm).

For each subject of each study treatment arm, amounts of Na and K will be calculated by multiplying the respective concentration by the volume of urine for each collection interval. The individual ratio (Na/K) will then be calculated for each urine collection interval using the amounts of Na and K. The corresponding logarithm of the Na/K ratio will be determined. To avoid negative values, ratio will be multiplied by 10 before transformation, i.e., $\log_{10}(10*Na/K)$).

In cases where the subject was not able to urinate the urine volume is set to zero. In cases where the subject is not able to urinate and/or concentration of Na and/or K is missing, the concentrations, the amounts and both ratios will be set to be missing. In cases where concentrations of Na and/or K is <LLOQ, the concentrations will be set to ½ LLOQ for calculation of the ratio.

13.2. Presentation of Data

Urine volume, concentration and amount of Na and K as well as the ratio (Na/K) and the corresponding logarithm of the ratio ($\log_{10}(10*Na/K)$) will be listed. These data except urine volume will be tabulated by study treatment arm for each collection interval.

The following statistics will be calculated for concentrations: number of measurements, arithmetic mean, standard deviation and CV, minimum, median, maximum value, geometric "n", geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and geometric CV. For amounts as well as ratios, only arithmetic statistics will be provided.

Time curves of both individual and arithmetic mean of $\log_{10}(10*Na/K)$ versus time (urinary collection interval) will be plotted by study treatment arm. The scheduled sampling time interval will be used for both individual and mean plots. Values of $\log_{10}(10*Na/K)$ will be plotted at the end of each scheduled sampling time interval. The same rules of handling concentrations below LLOQ as defined above will be applied for the plots.

13.3. Analysis of Pharmacodynamic Parameters

PD parameters will be summarized descriptively for each study treatment arm (i.e., vamorolone, eplerenone, and negative control arm) as mentioned above in Section 13.2.

A comparison of logarithm of the ratio (log10(10*Na/K)) will be made to evaluate MRA effect of the treatment arms "Vamorolone" versus "Eplerenone" and "no treatment", by performing a Random Effects Model analysis using PROC MIXED of SAS®. The model will include TIME POINT and TREATMENT and their interaction, and SUBJECT as random effect. The results (least-squares [LS] means, difference between LS means, and 90% CIs of the difference) will be presented by timepoint.

14. SAFETY ANALYSES

14.1. Adverse Events

Definition of AE are in protocol section 8.4. AEs will be coded using the medical dictionary for regulatory activities (MedDRA) dictionary, using the version reported in the Data Manual Plan.

For each subject within a study treatment arm, AEs that continue with changing intensity will be counted as one AE and only the worst severity will be considered in the corresponding frequency tables. Moreover, a recurrent AE (e.g. a headache for a couple of hours each day) will be counted as several AEs.

A listing of AEs according to the ICH Guidelines will be created. This listing will include, at minimum, a description of AEs as coded and reported, last study treatment administration date and time (including relative day), start/end time and date of occurrence (including relative day), time lag (onset) since last administration of study treatment (provided for all study treatment arms), duration, seriousness, severity, relationship to study treatment separate for each study treatment arm, other causality factors, concomitant medication taken (yes, no), concomitant procedure done (yes, no), outcome, and action taken (provided for all study treatments).

Fludrocortisone will be given before first administration of vamorolone, eplerenone, or corresponding time point for the negative control arm, therefore the AEs in this time period will be displayed separately in listings and summary tables.

All analyses will be restricted to treatment-emergent AEs (TEAEs), defined as all AEs that emerge during treatment and having been absent pre-treatment or worsening relative to the pre-treatment state. All other AEs will be listed only and defined as pre-treatment AEs.

A frequency table will be compiled showing the number and percentage of subjects per study treatment arm affected by
- any TEAE
- any study treatment related TEAE (related to vamorolone, eplerenone, or fludrocortisone)
- any vamorolone/eplerenone related TEAE
- any fludrocortisone related TEAE
- any mild, moderate, and severe TEAE
- any study treatment related severe TEAE
- any vamorolone/eplerenone related severe TEAE
- any fludrocortisone related severe TEAE
- any serious TEAE
- any TEAE leading to death
- any study treatment related TEAE leading to death.

This table will also show the frequencies of the events per study treatment.

Further summary tables will be generated by study treatment arm. These tables will be sorted by system organ class and preferred term. The numbers and percentages of subjects with AEs and the frequency of the events will be reported. Three sets of such summary tables by study treatment arm will be presented:
- overall

- by relationship (see definition above)
- by severity.

14.2. Clinical Laboratory Examinations

Laboratory data will be listed by subject, study treatment, and study time. Variables: at minimum scheduled study time, date, laboratory parameter, unit, results at each of the assessment times, comments (if available). Values outside of normal ranges as well as clinically relevant values will be highlighted or annotated.

Another listing will show date and clock times of laboratory sampling.

Separate listings for abnormal laboratory values as well as abnormal laboratory values considered clinically relevant by the investigator will also be provided.

Laboratory abnormalities considered clinically relevant by the investigator will also be reported as AE and therefore listed in the AE listings.

14.3. Vital Signs

Vital Signs will be listed by subject, study treatment arm, and study time. Variables: at minimum scheduled study time, date, clock time, location of measurement, parameter (systolic blood pressure, diastolic blood pressure, pulse rate, body temperature), interpretation, and comments (if available).

Descriptive statistics of vital signs will be presented for each scheduled time by study treatment arm.

Arithmetic mean curves (with standard deviation) over time of vital signs by study treatment arm will also be provided.

A separate listing will be created for body weight at screening, Day -2, und Day 4.

14.4. Electrocardiograms

ECG parameters (PR(Q) interval, QRS duration, QT interval uncorrected, QT interval corrected according to the formula of Fridericia (QTcF), Heart Rate), interpretation (normal/abnormal, clinical significance), comments (if available) will be listed by subject, study treatment arm, and study time.

Descriptive statistics will be presented for PR(Q), QRS, QT, QTcF and Heart Rate for each scheduled study time by study treatment arm.

The ECG interpretation will be tabulated as the number and percentage of subjects with “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant” results by study treatment arm and scheduled study time.

14.5. Physical Examination

Any findings will be reported as medical history or adverse event.

14.6. Drug Administration and Pharmacokinetic Plasma and Pharmacodynamic Urine Sampling

Duration as well as the number of administrations of each study treatment will be calculated, listed, and summarized for each study treatment arm.

An exposure listing will be provided by subject, study treatment arm, study treatment, and scheduled study time. This listing will contain, at minimum, the calculated study treatment duration as well as number of administrations, actual dose, unit, route, dose formulation, vamorolone bottle weights, change in dose and reason, dose adjusted and reason, no dose and reason.

A separate listing of PK plasma sampling including time deviations from scheduled sampling times will be provided sorted by subject in study treatment arm 1 (vamorolone dosing) and study treatment arm 2 (eplerenone dosing).

Time deviations (hh:mm) for plasma samplings will be calculated as

time deviation = actual sampling date and time – scheduled sampling date and time.

The actual date and time (24-hour clock time) of each sample will be recorded. Allowed assessment time windows will be defined in the deviation manual and collected in the quality issue log (see Section 7).

Any time deviations falling into the allowed time windows will not be considered a protocol deviation. PD urine collection including time deviations from scheduled sampling time, and urine volume of each sample will be provided sorted by subject in each study treatment arm.

15. OTHER ANALYSES

Not applicable.

16. INTERIM ANALYSES

Interim analyses are not anticipated.

17. CHANGES TO PROTOCOL PLANNED ANALYSES

The SAP confirms to the study protocol and its amendment(s).

18. GENERAL FORMAT OF TABLES, FIGURES AND SUBJECT DATA LISTINGS

There are no Sponsor-specific guidelines or SOPs that must be observed for the analysis or report generation.

The standard report is an integrated study report according to Nuvisan SOPs and ICH-guidelines. The Sponsor does not require any specific formats (e.g. footer, header, margins, fonts) to be observed. The tables, listings, and figures (TLFs) provided for the report will be formatted with font courier new with at least 7 points.

Study treatment labels to be used in TLFs will be:

Arm 1: Single Oral Dose of 20 mg/kg Vamorolone with Fludrocortisone Administrations

Arm 2: Single Oral Dose of 200 mg Eplerenone with Fludrocortisone Administrations

Arm 3: Negative Control Arm with Fludrocortisone Administrations

For AEs only occurring prior to first administration of vamorolone, eplerenone, or corresponding time point for the negative control arm:

F: 1 mg Fludrocortisone

The following lists in Section 19 provide an overview of a possible Table of Contents (TOC) of the outputs produced for statistical analysis.

19. APPENDIX

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* Defines the listings for DRM.

20. References

Not applicable.