A Phase 1, Three-Part, Open-Label Study to Assess the Safety, Tolerability and Pharmacokinetics of Single Doses of Inhaled Voriconazole (ZP-059) in Healthy Subjects (Part 1), Multiple Doses of ZP-059 in Mild Stable Asthma Subjects (Part 2) and in a Two-Period Crossover Study of Single Doses of ZP-059 and Single Doses of Oral Voriconazole in Mild to Moderate Stable Asthma Subjects (Part 3)

Zambon Study No: Z7240J01
Syne qua non Ltd Study No: MET19010

Statistical Analysis Plan

Version: 2.0

Date: 28 October 2020

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Paula McSkimming

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Arnd Mueller

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Modification History

Version	Change History	Reason	Date
1.0	First Version	N/A	12AUG2020
2.0	1. Update to protocol deviations listing to only important PDs 2. Removed exposure table from analysis 3. Updated AESI to tabulate if necessary 4. Added Sputum plug and processed sputum to analysis	1. To bring in line with SQN current processes 2. Following client review of dry run TFL	28OCT2020

Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC_{0-t}	Area Under the Concentration time curve over the Dosing Interval
AUC_{0-inf}	Area Under the Concentration time curve from time Zero to Infinity
AUC_{tau}	Area Under the Concentration curve from time Zero to the End of the dosing period
BLQ	Below limit quantification
BMI	Body Mass Index
CI	Confidence Interval
CL/F	Apparent total clearance of the drug from the serum
C_{min}	Minimum Observed Concentration
C_{max}	Maximum Observed Concentration
$C_{max,ss}$	Maximum Observed Concentration following drug administration at a steady state
CS	Clinically Significant
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GMR	Geometric Mean Ratio
IMP	Investigational Medicinal Product
K_{el}	Apparent First-Order Terminal Elimination Rate Constant
Log_e	Natural Logarithm
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
NC	Not calculated
NCS	Not Clinically Significant
NR	No Result
PEFR	Peak Expiratory Flow Rate
PK	Pharmacokinetic
PT	Preferred Term

R_{ac}	Accumulation Ratio
SAC	Safety Advisory Committee
SAD	Single Ascending Dose
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
$t_{1/2}$	Terminal Elimination Half-Life
TEAE	Treatment Emergent Adverse Event
t_{max}	Time of the Maximum Observed Concentration
$t_{max,ss}$	Time of the Maximum Observed Concentration following drug administration at a steady state
ULN	Upper Normal Limit
Vz/F	Volume of Distribution During Terminal Phase After Non-Intravenous Administration
WHO Drug	World Health Organization Drug Dictionary
% fluctuation	Percentage Fluctuation Over the Dosing Interval
% swing	Percentage Swing Over the Dosing Interval

1 INTRODUCTION

This document details the statistical analysis that will be performed for the Zambon study: A Phase 1, Three-Part, Open-Label Study to Assess the Safety, Tolerability and Pharmacokinetics of Single Doses of Inhaled Voriconazole (ZP-059) in Healthy Subjects (Part 1), Multiple Doses of ZP-059 in Mild Stable Asthma Subjects (Part 2) and in a Two-Period Crossover Study of Single Doses of ZP-059 and Single Doses of Oral Voriconazole in Mild to Moderate Stable Asthma Subjects (Part 3).

The proposed analysis is based on the contents of the Final Version of the protocol (dated 13th December 2019), amendment 1 (dated 14th February 2020) and amendment 2 (dated 04 June 2020). 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 CHANGES FROM THE PROTOCOL PLANNED ANALYSIS

For the PK analysis, linearity ratios will not be reported due to the likelihood that AUC_{0-inf} cannot be obtained.

3 STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

3.1.1 Primary Objectives

The primary objectives of the study are:

- Part 1: To determine the safety and tolerability of single inhaled doses of ZP-059 in healthy subjects.
- Part 2: To determine the safety and tolerability of multiple inhaled doses of ZP-059 in subjects with mild stable asthma.
- Part 3: To determine the safety and tolerability of single inhaled doses of ZP-059 and Oral Voriconazole in subjects with mild to moderate stable asthma.

3.1.2 Pharmacokinetic (PK) Objectives

The PK objectives of the study are:

- Part 1: To characterise systemic PK of voriconazole and N-oxide voriconazole after single doses of ZP-059 in healthy subjects.
- Part 2: To characterise systemic PK of voriconazole and N-oxide voriconazole after multiple doses of ZP-059 in subjects with mild, stable asthma.
- Part 3: To characterise systemic PK of voriconazole and N-oxide voriconazole after single doses of ZP-059 and single doses of oral voriconazole in subjects with mild to moderate stable asthma.

3.1.3 Exploratory Objectives

The exploratory objectives of the study are:

- Part 1: None
- Part 2: To characterise voriconazole and N-oxide voriconazole concentrations in induced sputum after multiple doses of ZP-059 (i.e. on Day 7; both pre-dose and post-dose) in subjects with mild, stable asthma.
- Part 3: To characterise voriconazole concentrations and N-oxide voriconazole in induced sputum after single inhaled doses of ZP-059 and after single doses of oral voriconazole in subjects with mild to moderate stable asthma.

3.2 Study Endpoints

3.2.1 Primary Endpoints

The primary endpoint for each Part (Part 1, 2, & 3) of the study is:

- Safety and tolerability, as assessed by monitoring of adverse events (AEs), physical examinations, changes in vital signs, clinical laboratory parameters, electrocardiogram (ECG), pulse oximetry and spirometry assessments (forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEFR) and FEV_1/FVC).

3.2.2 Pharmacokinetic (PK) Endpoints

The PK endpoints to analyse both voriconazole and N-oxide voriconazole for each part (Part 1, 2, & 3) of the study are:

- Parts 1, 2 and 3 (in Part 3, Day 1 of Treatment Period 1 and Day 1 of Treatment Period 2):
  - AUC_{0-t}; where 't' is the last timepoint at which concentrations were quantifiable, nominally 12 h, 24 h & 96 h for Parts 1, 2 and 3 respectively. Note that the last timepoint, t, may differ depending on the actual data and dose regimen.
  - AUC_{0-inf}. Note that if dosing is twice daily robust estimation of AUC_{0-inf} on Day 1 part 2 may prove challenging.
  - AUC_{tau}; Part 2, Day 1 only
  - C_{max}
  - t_{max}
  - K_{el}; except Part 2 (day 1)
  - $t_{1/2}$; except Part 2 (day 1)

- Part 2 (Day 10):
  - AUC_{tau},
  - $C_{max,ss}$
  - $t_{max,ss}$
  - $C_{ss,av}$
  - %fluctuation and swing (as appropriate and when applicable)
  - Accumulation (R_{ac}) based on the ratio of Day 10 AUC_{tau} to Day 1 AUC_{tau}
  - Pre-dose concentrations measured on Days 3 to 10 will be designated as C_{min} values

- For voriconazole only CL/F and Vz/F will be estimated from Part 1, Part 2 (Day 10) and Part 3 serum concentration data

These will be assessed using the serum concentration for voriconazole and N-oxide voriconazole.

3.2.3 Exploratory Endpoint(s)

The exploratory endpoint for Parts 2 & 3 of the study is:

- Induced sputum concentrations dependent on data availability of voriconazole and N-oxide voriconazole on Day 7 for Part 2 and Days 1, 2 and 3 of each treatment period for Part 3

3.3 Study Design

This is an integrated Phase 1, single centre, multi-part, open-label study in both healthy subjects (Part 1), subjects with mild stable asthma (Part 2) and subjects with mild to moderate stable asthma (Part 3).

Part 1 is comprised of 4 separate cohorts containing 6 subjects each. Each subject will receive a single dose of ZP-059 with the dose increasing per cohort following review of safety data from the preceding cohort. The study will have an interleaved design. A further cohort may be enrolled if deemed appropriate to repeat a dose level, assess an interim dose or a dose higher than planned.

Part 2 is comprised of 3 separate cohorts containing 6 subjects each. The treatment period will be for 10 consecutive days with each subject receiving daily doses of ZP-059 (either once daily for 10 days, or twice daily for the first 9 days and once on Day 10), of which the dose and frequency is determined following a safety review of the data from Part 1 Cohort 2. Dose escalation in the next cohort will proceed following completion of the safety assessments 24 hours post dose on Day 10 for a minimum of 4 subjects. A further 2 cohorts may be enrolled if deemed appropriate to repeat a dose level, assess an interim dose, a different dosing regimen or a dose higher than planned.

Part 3 is a two period, randomised crossover study in 16 subjects with a minimum of 6 sputum producers and comprises of 2 cohorts to receive a single dose of ZP-059 in one period, of which the dose is determined following a safety review of the data from Part 1 (Cohorts 1 to 4), and a single dose of 200mg oral voriconazole in the other period. Subjects are randomised to the sequence in which they receive treatment. There will be a minimum wash out period of 96 hours between treatments. Dosing of Part 3 may occur prior to or in parallel with Part 2 of the study.

Further details of the study design can be found in section 4 of the protocol.

3.4 Visit Structure

The visit structure and the schedule of activities for each part of the study are detailed in section 1.2 of the protocol. Details of the residential stays, study assessments and procedures at each visit can be found in section 8 of the protocol.

4 SAMPLE SIZE

Part 1 (Single Ascending Dose (SAD) - Healthy subjects) and Part 2 (Multiple Ascending Dose (MAD) – Mild, Stable Asthma Subjects):

This study is not powered for any formal hypothesis test. The sample size of up to 30 subjects (24 subjects plus an additional 6 subjects in 1 optional cohort) in Part 1 and up to 30 subjects (18 subjects plus additional 12 subjects in 2 optional cohorts) in Part 2 was chosen to minimise exposure to Investigational Medicinal Product (IMP) while allowing an adequate assessment of safety at each dose in order to support dose escalation and an adequate number of subjects to assess mean PK parameters. A minimum of 4 evaluable subjects will be required for each cohort for both dose escalation decisions and assessment of mean PK parameters.

Part 3 (Mild to Moderate, Stable Asthma Subjects):

This study is not powered for any formal hypothesis test. A sample size of up to 16 subjects was chosen to minimise exposure to IMP while allowing an adequate assessment of safety, PK parameters and drug concentration in sputum. No replacements are foreseen. However, should the drop-out rate for non-safety reasons be high, which may compromise the reliability of the study results, additional subjects could be randomised.

5 RANDOMISATION AND BLINDING

Subjects will only be randomised in Part 3 of the study. They will be randomised in a 1:1 fashion to the sequence in which they will receive treatments for the crossover design. There will be no stratification.

As this is an open-label study, no blinding is required.

6 INTERIM ANALYSIS

No interim analysis is planned.

Interim safety data reviews will be held to make decisions on the dose escalations during Parts 1 & 2 and the dose of ZP-059 to administer in Parts 2 (starting dose) and 3 of the study. The reviews are conducted by the safety advisory committee (SAC) which is made up of the Principal Investigator ((PI) or delegate) and the sponsor's medical monitor as a minimum. Further details are available in section 6.6 of the protocol.

No outputs will be produced by SQN for these reviews.

7 ANALYSIS PLAN

7.1 General

Summary statistics for continuous variables will consist of the number of non-missing observations (n), mean, standard deviation (SD), minimum, 25th percentile, median, 75th percentile 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 subjects in each category will be presented, based on the number of non-missing observations apart from the disposition of subjects, protocol deviations, background and demographic characteristics, prior and concomitant medications/procedures and AEs where the percentage will be based on the number of subjects in the analysis set.

The number of missing observations will also be presented for each variable.

7.2 General Derivations

This section provides details of general derivations. Derivations specific to the parameter of interest are detailed within the specific SAP section.

7.2.1 Baseline

For Parts 1 & 2 of the study, baseline is defined as the pre-dose value on Day 1. If that is missing it will be defined as the last non-missing value prior to the subject receiving study treatment (pre-dose) on Day 1.

For Part 3 of the study, within-period baseline is defined as the last non-missing value (including scheduled and unscheduled assessments) pre-dose on Day 1 for each of the respective study treatments. Overall baseline is defined as the pre-dose value on Day 1 of Period 1. If that is missing it will be defined as the last non-missing value prior to the subject receiving study treatment (pre-dose) on Day 1.

7.2.2 Study Day

Throughout this SAP any references to “Day XX” refer to the pre-specified visits defined in the protocol (where the study treatment administration visit is Day 1).

Data listings by visit will additionally present study day. Study day will be calculated relative to the first date of administration of study treatment (Study Day 1). For Part 3, the treatment period (Period 1/Period 2) and period day will also be referenced as per section 7.2.3.

7.2.3 Period and Period Day

Period is defined as a subject’s treatment window, where Period 1 relates to the treatment period of the first study treatment received by the subject and Period 2 refers to the treatment period of the second study treatment received by the subject.

For the purposes of reporting, data collected from the administration of first study treatment in Period 1 until the day prior to administration of first study treatment in Period 2 will be assigned to Period 1. Data collected on or after the day of the administration of first study treatment in Period 2 will be assigned to Period 2.

Period day will be calculated relative to the first date of administration of study treatment in each period. Data listings by visit will additionally present period and study day where appropriate.

7.2.4 Treatment Start and End

Treatment start is defined as the first day of administration of study drug (Day 1) for Parts 1 & 2 of the study. For Part 3, Treatment start is defined as Day 1 of treatment period 1.

In Part 1 of the study, treatment is received as a single dose therefore treatment end is also Day 1.

For Part 2, treatment end is defined as the final day of administration of study drug which is scheduled as Day 10.

In Part 3, treatment is received as a single dose within the treatment period therefore treatment end is Day 1 of treatment period 2.

7.2.5 Planned dose and actual dose received

Planned dose of study drug depends on the cohort to which the subject was enrolled and will be determined by the SAC. Actual dose received is defined as the actual dose of study drug received regardless of enrolled cohort and is recorded on the electronic Case Report Form (eCRF).

7.2.6 Incomplete Dates

For calculation purposes, incomplete dates will be completed using worst-case, the most conservative value possible. For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations. If day is missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month and year components.

7.2.7 Non-Numeric Values Recorded in Numeric Fields

In the case where a variable is recorded as “>x”, “≥x”, “<x” or “≤x” rather than an exact number, 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.

7.3 Missing Data and Withdrawals

In general, data will not be imputed. Where imputation may be deemed appropriate, information is detailed in the analysis descriptions.

7.4 Analysis Sets

The **Screened Set** includes all subjects screened for the study irrespective if they were enrolled into the study.

The **Enrolled Set** includes all subjects who passed screening irrespective of whether they received the study treatment.

The **Safety Analysis Set (SAF**) will consist of all subjects who receive at least one dose of study treatment. Subjects will be analysed according to the treatment actually taken.

The **PK Concentration Set** will consist of those subjects in the SAF who have at least one quantifiable serum PK concentration recorded. Subjects will be analysed according to the treatment actually taken.

The **PK Parameter Set** will consist of those subjects in the SAF with sufficient concentration time data to determine at least one quantifiable serum PK parameter. Subjects will be analysed according to the treatment actually taken.

The **PK Sputum Concentration Set** will consist of those subjects for Parts 2 & 3 in the SAF who have at least one quantifiable induced sputum PK concentration recorded. Subjects will be analysed according to the treatment actually taken.

All protocol deviations will be assessed by Zambon and documented on a case-by-case basis prior to the database lock, and important deviations considered having a

serious impact on the PK analysis will lead to the relevant subject being excluded from the relevant sets.

The definitions for the analysis sets are sufficient to determine the subjects included within these analysis sets and so do not require listing and agreeing prior to database lock.

For Part 3 of the study, planned study treatment sequence will be determined from the randomisation list. Actual treatment received will be derived by reconciling the kit number entered in to the CRF with the kit list supplied by Zambon.

7.5 Data presentations

7.5.1 Parts 1 & 2 Specific Presentations

For each study part, safety and PK data will be summarised by ZP-059 dose only and all other data will be summarised in tabular form by ZP-059 dose group and overall.

Listings will be sorted by study part, ZP-059 dose group, screening number and date/time of assessment.

Dose groups will be presented in the following order using these labels:

- ZP-059 5mg
- ZP-059 XXmg, etc.

7.5.2 Part 3 Specific Presentations

Safety and PK data will be summarised by treatment group and all other data will be summarised in tabular form by treatment sequence and overall.

Listings will be sorted by treatment or treatment sequence as appropriate, screening number and date/time of assessment.

Treatment groups will be presented in the following order using these labels:

- ZP-059
- Oral Voriconazole

Treatment sequences will be presented in the following order using these labels:

- ZP-059 / Oral Voriconazole
- Oral Voriconazole / ZP-059

7.5.3 General Presentations

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

Only scheduled post-baseline assessments will be tabulated; post-baseline repeat/unscheduled assessments will not be tabulated, although they will be listed.

Eligibility, screen failures and analysis sets will be summarised using the Screened set. Background and demographic characteristics, study completion/withdrawal, and protocol deviations will be summarised using the Enrolled Set. Prior/concomitant medications, administration of study treatment and exposure and safety will be summarised using the SAF.

All other data will be summarised using the SAF apart from PK, which will be summarised using the relevant PK sets.

Eligibility and screen failures will be listed using the Screened set. Completion/withdrawal and analysis set listings will be based on the Enrolled set. PK listings will be based on the PK sets. Safety listings will be based on the SAF set. All other listings will be based on the Enrolled set.

7.6 Disposition of Subjects

The number of all screened subjects will be presented overall. The number and percentage of all subjects enrolled and included in the SAF and PK analyses sets who completed the study and prematurely discontinued the study, who completed study treatment and prematurely discontinued study treatment, study duration and treatment duration (Part 2 only), will be summarised. The number and percentage of subjects will be summarised by their reasons for withdrawal from the study and study treatment.

Study duration will be derived as the number of days between study Day 1 and the date of study completion or the date of early study withdrawal.

Eligibility for each of the analysis sets along with reasons for exclusion will be listed. Inclusion and exclusion criteria will be listed. Study completion/withdrawal data will be listed. Informed consent date and the protocol version enrolled under will also be listed.

7.7 Protocol Deviations

Prior to database lock, Zambon will provide the individual deviations and their classifications prior to database lock and analysis set assignment.

Details of all important protocol deviations (date, deviation group, deviation category and specific details) will be listed.

7.8 Background and Demographic Characteristics

7.8.1 Demography

Demographic characteristics (age, sex, and race), body measurements (height, weight and body mass index (BMI)) collected at Screening and time since diagnosis of asthma (Parts 2 & 3 only) will be summarised. For part 3, asthma severity will also be summarised.

Age is calculated in years on the date of first administration of study treatment.

BMI will be reported using the values entered into the eCRF.

Time since asthma diagnosis is derived using the date of informed consent.

All subject demographic data including informed consent will be listed.

7.8.2 Smoking History

Smoking history data will be listed only.

7.8.3 Medical History

Medical history events (not including asthma diagnosis) will be coded using the latest Medical Dictionary for Regulated Activities (MedDRA) dictionary version. The version used will be indicated in the data summaries and listings. The number and percentage of subjects will be presented for ongoing conditions and previous conditions (stop date prior to screening) 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 subjects with medical history events. Subjects will only be counted once per SOC and PT term. All events will be listed.

7.9 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 taken within 28 days prior to screening. Medications that are ongoing at screening or started after screening 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.

For Part 3, the following rules will be used to define whether a medication is concomitant and which treatment they should be assigned to:

- Concomitant to Period 1 only is defined as medication administered from first administration of study drug for Period 1 and finishing prior to the first administration of study drug for Period 2.
- Concomitant to Period 2 only is defined as starting from first administration of study drug in Period 2.
- A treatment starting before the end of Period 1 and continuing into Period 2 will be reported under both periods.
- If medication dates are incomplete and it is not clear whether the medication was concomitant to a single treatment period, it will be assumed to be concomitant to both periods

The number and percentage of subjects taking concomitant medications will be summarised by medication class and standardised medication name, where medication class and standardised medication name will be presented alphabetically. In summary tables, subjects 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.

Prior and concomitant medication data will be listed and flagged accordingly.

7.10 Administration of Study Treatment and Exposure

Details of the timings of treatment administration will be listed along with the number of doses of study treatment administered, total exposure, and the number and cause of dose interruptions. This will be listed by treatment period for Part 3 and include the treatment received.

7.11 Efficacy Analysis

Not applicable.

7.12 Pharmacokinetics

7.12.1 Serum concentrations

Serum concentrations of both voriconazole and N-oxide voriconazole will be summarised over time and listed for those in the PK Concentration set. Mean, SD, minimum, maximum and median will be presented.

Similar analyses will be completed for the PK parameters listed in section 3.2.2 for those subjects in the PK Parameters set. Additionally, the geometric mean, CV% and geometric SD will also be presented.

Mean (±SD) serum concentration profiles will be plotted on the original scale and on the log scale. Samples below limit of quantification (BLQ) prior to the first quantifiable concentration will be set to zero. Samples with concentrations BLQ after the first quantifiable concentration will be set to 'missing' and omitted from the analysis. Other PK parameters will be calculated according to standard equations.

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and in the clinical study report. The following conditions for PK parameter inclusion may also be applied:

- $AUC_{0\text{-}inf}$, k_{el}, $t_{½}$, CL/F (exception Part 2, Day 10) and Vz/F to be excluded if the regression does not include at least 3 different time points in the terminal phase (after C_{max}, but excluding the concentration at t_{max})
- $AUC_{0\text{-}inf}$, CL/F (exception Part 2, Day 10) and Vz/F, $t_{½}$, k_{el} to be excluded if the coefficient of determination, Adjusted R^2 in the regression, is less than 0.8
- $AUC_{0\text{-}inf}$, CL/F and Vz/F is excluded if the %extrapolated area is greater than 20% (exception CL/F and Vz/F in Part 2, Day 10)

Metabolite parent ratios will be estimated for C_{max} and AUC across all parts of the study.

The following rules will be applied if there are BLQ or missing values (e.g. no result (NR)) in serum concentration data series to be summarised:

- If an embedded BLQ value was set to missing for PK analysis, this value will be excluded from the summary statistics. Other BLQ values will be set to 0.
- NR results will be set to missing.
- If all the values are BLQ, then the arithmetic mean, arithmetic standard deviation (SD), median, min and max will be presented as zero, and the geometric mean and geometric coefficient of variation (CV) will be denoted as NC (not calculable).

The PK parameters will be listed together with the sample collection details for each study Part.

7.12.2 Induced Sputum Concentrations

For subjects in the PK Sputum Concentration set for Parts 2 (Day 7) and 3 (Days 1, 2 and 3 for each treatment period) of the study, induced sputum plug and processed sputum concentrations of voriconazole and n-oxide voriconazole will be listed. Where there is sufficient data, induced sputum plug and processed sputum concentrations and PK parameters of voriconazole and n-oxide voriconazole may be summarised

over time. Mean (±SD) induced sputum concentration profiles may also be plotted on the original scale and on the log scale.

7.12.3 Dose proportionality

Dose proportionality of ZP-059 will be assessed by fitting a power model as follows:

$$log_{10}(y) = \alpha + \beta\ log_{10}(dose)$$

Where α represents the random subject effects for intercept and dose. A value of 1 for β indicates perfect dose proportionality. Therefore, the estimate of β together with the corresponding 90% confidence interval (CI) will be used to quantify dose proportionality. The increase in concentration over the dose range will be estimated by the ratio of the expected concentration with the highest dose to that of the lowest dose. This will be derived by back-transforming the difference on the log10 scale between the two doses and will be accompanied by its associated 90% confidence interval. If the exposure is dose proportional there should be a fold increase equal to the ratio of highest: lowest dose across the dose range.

If it isn't possible to fit random subject slopes a common fixed effect slope will be fitted.

Dose proportionality will be assessed for each of the following PK endpoints for voriconazole and n-oxide voriconazole separately:

- C_{max}
- $AUC_{0\text{-}t}$, where t is 12 hours for Part 1, 24 hours for Part 2 and 96 hours for Part 3.
- $AUC_{0\text{-}inf}$

These will be performed separately for Part 1 and Part 2 at Day 1 and Day 10. This analysis will be performed if 3 or more dose levels are used for the Part.

Dose proportionality will also be assessed using an analysis of variance (ANOVA) method. A mixed effects model will be fitted with fixed effects for dose and random effects for subject. The difference between the dose levels will be presented along with a 90% confidence interval and p-value.

7.12.4 Bioavailability

The PK endpoints (see Section 7.12.3) estimated from Part 3 of the study will be analysed to assess relative bioavailability of Inhaled Voriconazole (ZP-059) to Oral Voriconazole (VFEND®) by fitting a mixed effects analysis of variance (ANOVA) model to the log_e transformed PK parameter including fixed effect terms for treatment, period, sequence and sex and a random effect term for subject (nested within sequence). The adjusted geometric mean ratio (GMR) (Inhaled: Oral) and the corresponding 90%confidence interval (CI) for the adjusted GMR will be presented.

In addition, the PK endpoints will be compared between asthma subjects in Part 3 and healthy subjects in Part 1 and separately with asthma subjects in Part 2 to assess relative bioavailability of the Inhaled Voriconazole (ZP-059) dose taken in Part 3 in these populations. An ANOVA model will be fitted to the log_e transformed PK

parameter including terms for the population group (i.e., healthy subjects or asthma subjects) and sex. The adjusted GMR and 90% CI for the adjusted GMR for the comparison between the two populations for the relevant dose will be provided, where the ratio is defined as either Part 3 subjects/Part 1 subjects or Part 3/Part 2 subjects, depending on the comparison.

7.13 SAFETY EVALUATION

The safety and tolerability of ZP-059 will be assessed based on AEs, clinical laboratory assessments, vital signs, ECGs, pulmonary function and pulse oximetry parameters.

Details regarding the evaluation of these data are given in the following respective sections.

7.13.1 Adverse Events

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

7.13.1.1 Treatment-emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as an AE that started on or after the start of the administration of 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.

In Part 3 of the study, AEs are treatment emergent and accountable to the Period 1 treatment if they started on or after the start of the administration of study treatment in Period 1 up to the first administration of study treatment in Period 2. For Period 2, AEs are treatment emergent and accountable to the Period 2 treatment if they started on or after the start of the administration of study treatment in Period 2 up to the end of the follow-up period.

A treatment related TEAE is defined as a TEAE that is related to the study treatment. If the TEAE has a missing relationship it is assumed to be related to the study treatment for analysis purposes.

A summary table will present the following:

- TEAEs (events and subjects).
- Serious TEAEs (events and subjects).
- Serious study treatment related TEAEs (events and subjects).
- TEAEs by severity (mild/moderate/severe) (events and subjects).
- TEAEs by relationship to study treatment (events and subjects).
- TEAEs leading to withdrawal from study (subjects only).
- TEAEs leading to discontinuation of study treatment (subjects only).
- Study treatment related TEAEs leading to discontinuation of study treatment (subjects only).
- TEAEs leading to death (subjects only).

In the above summaries, if a subject experienced more than one TEAE, the subject will be counted once using the most related event for the “by relationship to study

treatment" and "related to study treatment" summaries, and by the worst severity for the "by severity" summary.

The following tables will be presented:

- TEAEs by SOC and PT.
    - If a subject experienced more than one TEAE assigned to the same treatment, the subject will be counted once for each SOC and once for each PT within that treatment .
- TEAEs by PT.
    - If a subject experienced more than one TEAE assigned to the same treatment, the subject will be counted once for each PT within that treatment .
- TEAEs by SOC, PT and severity.
    - If a subject experienced more than one TEAE assigned to the same treatment, the subject will be counted once for each SOC and once for each PT at the worst severity/CTC grade within that treatment .
- TEAEs by SOC, PT and relationship to study treatment and the related categories (related/unrelated).
    - If a subject experienced more than one TEAE assigned to the same treatment, the subject will be counted once for each SOC and once for each PT using the most related event within that treatment .

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

7.13.1.2 Adverse Events of Special Interest

An adverse event of special interest (AESI) is an AE of scientific and medical interest and is defined as an AE that started on or after the start of administration of study treatment to the end of the safety follow up period.

The following AESIs will be monitored during the study.

- Respiratory Events:
    - Moderate or severe dyspnoea/wheeze
    - Moderate or severe cough
    - Moderate or severe bronchospasm
- Moderate or severe visual impairment/hallucination
- Anaphylaxis and severe allergic reaction
- Hepatotoxicity ≥3X Upper Normal Limit (ULN) for Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and bilirubin
- COVID-19

If necessary, a summary table will present the following

- AESI (events and subjects).
- Non-serious AESIs (events and subjects).

- Serious AESIs (events and subjects).
- Serious study treatment related AESIs (events and subjects).
- AESIs by severity (mild/moderate/severe) (events and subjects).
- AESIs by relationship to study treatment (events and subjects).
- AESIs leading to withdrawal from study (subjects only).
- AESI leading to discontinuation of study treatment (subjects only).
- Study treatment related AESIs leading to discontinuation of study treatment (subjects only).
- AESIs leading to death (subjects only).

7.13.1.3 Adverse Event Listings

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

7.13.2 Clinical Laboratory Evaluation

Observed values and change from baseline in clinical chemistry, haematology, and urinalysis assessments will be summarised over time. If the test results are reported in categorical format, the results will be summarised by subject counts and percentage for each category. Parameters will be presented as recorded in the external data. Each clinical chemistry, haematology and urinalysis parameter will be classed as low, normal and high based on the reference ranges.

Clinical chemistry, haematology and urinalysis data will be listed separately including change from baseline and reference ranges. Flags will be populated to indicate all out of range values, classifications of values based on reference ranges and clinically significant values. Post-baseline unscheduled assessments will be also listed.

7.13.3 Vital Signs

Vital sign observed values and change from baseline by parameter will be summarised over time. Parameters will be presented in the same order as the eCRF. For vital signs data recorded on continuous scales, if more than one value is recorded at any one timepoint, the mean value will be presented.

All vital sign data will be listed including change from baseline and reference ranges with flags to indicate all out of range values.

7.13.4 Pulmonary Function (Spirometry)

Spirometry observed values and change from baseline by parameter will be summarised over time. Parameters will be presented in the same order as the eCRF.

All spirometry data will be listed including change from baseline and reference ranges with flags to indicate all out of range values.

7.13.5 Electrocardiography (ECG)

ECG observed values and change from baseline by parameter will be summarised over time. Parameters will be presented in the same order as the eCRF.

For data recorded on continuous scales, if more than one value is recorded per assessment, the mean value will be presented. For overall interpretation if more than one value is recorded per assessment, then the most severe of the respective readings will be taken.

All ECG results will be listed including change from baseline values and reference ranges with flags to indicate all out of range values and overall interpretation of the ECG (Normal, Abnormal Not Clinically Significant (NCS), and Abnormal Clinically Significant (CS)).

7.13.6 Physical Examination

Details of timings of physical examinations will be listed.

7.13.7 Pregnancy test

Pregnancy test details will be listed.

7.13.8 Urine Drug Screen

Urine drug test details will be listed. Parameters will be presented in the same order as the eCRF.

7.13.9 Alcohol Breath Test

Alcohol breath test details will be listed.

7.13.10 SARS-CoV-2 Test

SARS-CoV-2 test details will be listed.

7.14 References

Not applicable.

Document History

SignNow E-Signature Audit Log

All dates expressed in MM/DD/YYYY (US)

Document name: Z7240J01_MET19010_StatisticalAnalysisPlan_v2.0
Document created: 10/28/2020 12:06:41
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SignNow Web Application	Viewed the Document	deborah.ransom@synequanon.com	10/28/2020 12:14:41 pm UTC	10/28/2020 12:14:41 pm UTC	62.232.1.93
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SignNow Web Application	Viewed the Document	paula.mcskimming@synequanon.com	10/28/2020 13:19:06 pm UTC	10/28/2020 13:19:06 pm UTC	62.232.1.93
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