Clinical Study Protocol

Protocol Title:
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)

Protocol Number: Version Final 1.2, 04 June 2020

Amendment Number: 02 (Non Substantial)

Compound: ZP-059 (Inhaled voriconazole)

Study Phase: Phase 1

Short Title:
Phase 1 Three Part SAD, MAD & Cross-Over Study of ZP-059

Sponsor Name: Zambon S.p.A

Legal Registered Address: Via Lillo del Duca, 10, 20091 Bresso (Milan), Italy

Regulatory Agency Identifier Number:

EudraCT: 2019-004031-23

Approval Date: 04 June 2020

Sponsor Approvals:

Sponsor Signatory:

4th June 2020

Charlotte Keywood M.D.
Head of Open R&D, Zambon S.p.A.

Date

Medical Monitor's Name and Contact Information

Arnd Mueller MD, Clinical Development Physician, Zambon S.p.A.
Mobile +39 342 617 16.96
Email: arnd.muller@zambongroup.com

Drug Safety Unit, Zambon S.p.A.
Tel: +39 02 66524.444
Fax: +39 02 66524 038
E-mail: drugsafety@zambongroup.com

List of CRO and other Vendors

CRO:

MEU Solutions Ltd.	The Langley Building, Southmoor Road, Manchester, M23 9QZ, United Kingdom

Monitoring:

MEU Solutions Ltd.	The Langley Building, Southmoor Road, Manchester, M23 9QZ, United Kingdom

Participating site(s):

Medicines Evaluation Unit Ltd. (MEU)	The Langley Building, Southmoor Road, Manchester, M23 9QZ, United Kingdom

Safety Laboratory testing:

The Doctor's Laboratory (TDL)	The Halo Building, 1 Mabledon Place, London, WC1H 9AX, United Kingdom

Pharmacokinetic testing:

Alderley Analytical Ltd.	Alderley Park, Macclesfield, Cheshire, SK10 4TG, United Kingdom

Statistics and Data Management:

Syne Qua Non (SQN) Clinical	Gostling House, Diss Business Park, Hopper Way, Diss, Norfolk, IP22 4GT, United Kingdom

Investigator Signature Page

I have read this protocol.

I agree to comply with the current International Council for Harmonisation Guidelines for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved.

I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred or if any proceeding for debarment is pending or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the Health Authority/Ethics Committee/Institutional Review Board.

I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical study without the prior written consent of the sponsor.

Investigator Signatory:

S. D. Singh — 4 June 2020

Date

Name: Sukh Dave Singh

Title: Professor

Affiliation:
The Medicines Evaluation Unit (MEU) Ltd.
The Langley Building,
Southmoor Road,
Manchester,
M23 9QZ,
United Kingdom

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 02	04 June 2020
Amendment 01	14 Feb 2020
Original Protocol	13 Dec 2019

Amendment 02, 04 June 2020:
This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in this protocol amendment is to minimize the risk caused by the COVID-19 pandemic to research participants and site staff in this trial. These changes are in line with guidance from the Medicines and Healthcare products Regulatory Agency (MHRA) and NHS Health Research Authority (HRA) on the conduct of clinical trials during the COVID-19 pandemic and focus on assuring the safety of trial participants while maintaining compliance with good clinical practice (GCP) and minimizing risks to trial integrity.

Section # and Name	Description of Change	Brief Rationale
Throughout	Part 3 dosing can occur prior to Part 2 dosing.	Updated to provided clarification that dosing in Part 3 can not only be performed in parallel to dosing in Part 2 but also prior to.
1.1 Synopsis, 4.1 Overall Design, 5.3.1 Part 3 inclusion criteria 13, 8.11.7 Sputum induction	Minimum of 6 sputum producers to be enrolled in Part 3 of the study	Sputum PK is an exploratory endpoint in the study, only a minimum of 6 sputum producers instead of 16 will be required to meet study objective.
Throughout	+96hour post dose sputum removed from Part 3	Sputum PK is an exploratory endpoint in the study, +96hour sputum sample is not necessary from a PK perspective.
1.2.2. Schedule of Activities for Part 2, 5.2.1 Part 2 Inclusion criteria 12.	Inhaler device training at screening to be performed as a demonstration only.	Demonstration device training at screening is sufficient for asthmatic subjects in Part 2 & 3 as they can be considered as being well-trained in inhaler usage.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 4.1 Overall Design. 6.1 Administration of Investigational Products,	Optional BID dosing in Part 2 applicable for all cohorts	Updated to allow BID dosing in all Part 2 Cohorts and not just in Cohorts 4/5.
1.1 Synopsis, 4.1 Overall Design	For Part 3 minimum washout between Treatment Periods reduced to 96 hours. Residential stay extended to Day 6.	Reduced washout based on available PK data. Adapted residential stay to reduce risk of potential exposure to SARS-CoV-2 for both subjects and site staff.
2.3 Benefit/Risk Assessment, 4.1 Overall Design, 5.2.1 Part 2 Exclusion criteria 20. 5.3.2 Part 3 exclusion criteria 20, 8.1 Screening	SARS-COV-2 testing incorporated in Part 2 and Part 3	Due to the current COVID-19 pandemic SARS-COV-2 PCR testing, additional body temperature and other measures as applicable incorporated to reduce risk of potential exposure to SARS-COV-2 for both subjects and site staff.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Table of Contents

1. Protocol Summary

1.1. Synopsis

Study number	Z7240J01
Study title	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)
Number of centres and names	One centre in the UK: Medicines Evaluation Unit Ltd. (MEU) The Langley Building, Southmoor Road, Manchester, M23 9QZ, United Kingdom
Objectives	The primary **safety objectives** of the study are: <u>Part 1:</u> To determine the safety and tolerability of single doses of ZP-059 in healthy subjects. <u>Part 2:</u> To determine the safety and tolerability of multiple doses of ZP-059 in subjects with mild stable asthma. <u>Part 3:</u> To determine the safety and tolerability of single doses of ZP-059 in subjects with mild to moderate stable asthma. The **pharmacokinetic (PK) objectives** of the study are: <u>Part 1:</u> To characterize systemic PK of voriconazole after single doses of ZP-059 in healthy subjects. <u>Part 2:</u> To characterize systemic PK of voriconazole after multiple doses of ZP-059 in subjects with mild, stable asthma. <u>Part 3:</u> To characterize systemic PK of voriconazole after single doses of ZP-059 and single doses of oral voriconazole in subjects with mild to moderate stable asthma. The **exploratory PK objectives** of the study (Part 2 and Part 3 only) are: <u>Part 2:</u>

	To characterize 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 characterize voriconazole concentrations in induced sputum after single doses of ZP-059 and after single doses of oral voriconazole in subjects with mild to moderate stable asthma.
Summary of 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). In all parts of the study (i.e. Parts 1, 2 and 3) every effort will be made to include as close as possible an equal balance between male and female subjects; in Part 1 and Part 2 this will be in each of the individual cohorts. Safety, tolerability and PK will be assessed following either single ascending (SAD) or multiple ascending (MAD) dosing of ZP-059; Part 1 and Part 2, respectively. Part 1 will comprise 4 separate cohorts (each containing 6 subjects) planned to receive single doses of ZP-059. The starting dose for Cohort 1 will be 5 mg with subsequent doses being determined from review of safety data by the Safety Advisory Committee (SAC) from the preceding cohorts. The criteria to be followed by the SAC are detailed in Section 6.6.4. The study will have an interleaved design. Part 2 will comprise 3 separate cohorts (each containing 6 subjects) planned to receive daily doses of ZP-059 on Day 1 to 10. Dose levels for Part 2 will be determined from review of safety data from Part 1. Part 2 cohort 1 will commence after a review of safety data by the SAC from Part 1 cohort 2 confirms that it is safe to do so. The criteria to be followed by the SAC are detailed in Section 6.6.4. In each cohort, subjects will receive inhaled doses either once daily (QD) for 10 days or twice daily (BID) for 9 days and once in the morning of Day 10, as determined by the Sponsor based on data obtained in Part 1. Part 3 is a 2-period, randomised crossover study in 16 subjects with mild to moderate stable asthma to assess the safety, tolerability and PK of single doses of ZP-059 and single doses of oral voriconazole. Part 3 will comprise of 1 cohort randomised to receive ZP-059 and 200 mg of oral voriconazole administered across 2 treatment periods with a minimum wash-out period of 96 hours. The dose of ZP-059 for Part 3 will be confirmed after completion of SAD cohorts 1 to 4 and review of the available safety data. Hence, dosing of Part 3 may occur prior to/in parallel with dosing in Part 2. Subjects will be screened for eligibility to participate in the study within 28 days before dosing (Day 1) and will be admitted to the clinic on the evening of Day -1.

Further details of each study part are described below.

Part 1 (Single Ascending Dose)

Part 1 is a single ascending dose (SAD) study to assess the safety, tolerability and PK of single doses of ZP-059 in 4 cohorts of healthy male and female subjects. Each cohort will comprise 6 subjects (planned total of 24 subjects). An evaluable subject for Part 1 (SAD) of the study is defined as a subject who has received a dose of ZP-059 and has sufficient data to evaluate either the safety or PK objectives. An additional cohort of 6 subjects (Cohort 5) may be enrolled if it is deemed appropriate to repeat a dose level, assess an interim dose level or assess a dose level higher than planned (see Interim Data Reviews section). A repeat dose level or higher dose level will only be assessed provided no dose escalation or study stopping criteria have been met. Eligible subjects will receive a single dose of ZP-059 administered via dry powder inhaler (DPI) on the morning of Day 1. Subjects will be required to fast (water permitted) for at least 1 hour prior to each dose and 1 hour post each dose.

For the first 2 subjects in each cohort, there will be a minimum interval of 20 minutes between dosing. After the second subject is dosed there will be at least a 30 minutes observation period before the remaining 4 subjects are dosed. The remaining subjects will be dosed if the first two subjects show no clinically significant safety or tolerability concerns (including vital signs measurements, spirometry, physical examinations (symptom directed if required) and review of any adverse events [AEs] including any acute side effects e.g. excessive coughing) at the discretion of the investigator. Any clinically significant findings from the first two subjects in the opinion of the investigator will be discussed with the Sponsor prior to dosing of the remaining 4 subjects. The dosing interval between dosing subjects in the remainder of the cohort will be at the discretion of the investigator (in consultation with the sponsor if required) i.e. this could be increased or decreased as appropriate.

The fixed starting dose for SAD Cohort 1 is 5 mg (1 x 5 mg capsule*) ZP-059 single dose administered via DPI (RS01 monodose device) on Day 1. *Capsule delivers 5 mg of voriconazole. Subsequent doses in the following cohorts will be determined from review of safety data from the preceding cohorts.

Single doses will not exceed 40 mg of ZP-059 based on safety margins calculated following non-clinical studies. For each dose escalation, the dose increase will not be more than 3-fold. Details of ZP-059 (investigational medicinal product) are provided in the Investigational Medicinal Products section of the protocol.

Subjects will undergo safety, tolerability and PK evaluations at specified time points during the study. They will remain resident in the clinic until Day 2 after completion of safety assessments at 24 hours post-dose and providing there are no safety concerns, they will be discharged from the unit. A safety telephone call will be performed on Day 3 to check the status of unresolved AEs and to record any new AEs that have occurred after the last visit as well as any changes to concomitant

	medications. Subjects will return to the clinic on Day 5 for safety evaluations to be performed. A safety follow-up call will be performed 8 to 12 days post dose to check the status of unresolved AEs and to record any new AEs that have occurred after the last visit as well as any changes to concomitant medications. **Part 2 (Multiple Ascending Dose)** Part 2 is a multiple ascending dose (MAD) study to assess the safety, tolerability and PK of multiple doses of ZP-059 in 3 cohorts of male and female subjects with a physician confirmed documented diagnosis of mild stable asthma. Each cohort will comprise 6 subjects (planned total of 18 subjects). Up to 2 optional additional cohorts of 6 subjects (Cohort 4 and Cohort 5) may be enrolled in Part 2 if it is deemed appropriate to repeat a dose level, assess an additional dose level or assess a different dosing regimen, however, the dose will not exceed the highest dose studied in Part 1 (see Interim Data Reviews section). If a selected dose does not provide the required data to meet the objectives of the study, a previously tested dose may be used in a subsequent cohort. However, if the dose level met the dose escalation or study stopping criteria, neither that dose level nor a higher dose will be repeated. The planned starting dose of ZP-059 to be administered in MAD cohort 1 will be confirmed during an interim review of safety data from completed SAD cohorts and will not exceed a previously administered single dose. Dose administration for MAD cohort 1 will only commence after completion of review of safety data up to a minimum of 24 hours post-dose for the second dose level of Part 1 (SAD cohort 2). Dose levels for Part 2 will be determined from review of safety data from Part 1. Details of ZP-059 (investigational medicinal product) are provided in the Investigational Medicinal Products section of this synopsis. In each cohort, subjects will receive inhaled doses either once daily (QD) for 10 days or twice daily (BID) for 9 days and once in the morning of Day 10, as determined by the Sponsor based on data obtained in previous Part 1. In the event of QD dosing subjects will receive QD doses of ZP-059 (at Hour 0) on Days 1 to 10. In the event of BID dosing, ZP-059 will be administered at Hours 0 and 12 on Days 1 to 9 and once in the morning of Day 10 (i.e. 19 doses in total). Subjects will be required to fast (water permitted) for at least 1 hour prior to each dose and 1 hour post each dose; in the event of BID dosing this will be for both the 0 hour and the 12 hour doses. Following the first dose, subsequent doses will be administered within +/- 1 hour of the scheduled dosing time. If any of the additional cohorts (i.e. Cohorts 4 and 5) are required, subjects will receive either QD or BID doses, as may be appropriate. For the first 2 subjects in each cohort, there will be a minimum interval of 20 minutes between dosing (Day 1; Hour 0). After the second subject is dosed there will be at least a 30 minutes observation period before the remaining 4 subjects are dosed (Day 1; Hour 0). The remaining subjects will be dosed if the first two subjects show

	no clinically significant safety or tolerability concerns (including vital signs measurements, spirometry, physical examinations (symptom directed if required) and review of any adverse events [AEs] including any acute side effects e.g. excessive coughing) at the discretion of the investigator. Any clinically significant findings from the first two subjects in the opinion of the investigator will be discussed with the Sponsor prior to dosing of the remaining 4 subjects. The dosing interval between dosing subjects in the remainder of the cohort will be at the discretion of the investigator (in consultation with the sponsor, if required) i.e. this could be increased or decreased as appropriate. Subjects will undergo safety, tolerability and PK (serum and sputum) evaluations at specified time points during the study (a full serum PK profile will be collected on Days 1 and 10). They will remain resident in the clinic until the morning of Day 4 after completion of dosing and safety assessments and providing there are no safety concerns. The subjects will then return to the clinical unit daily from Day 5 through to Day 9 for pre-dose study procedures and to receive their scheduled dose (Hour 0) of study medication. On Day 7 the visit will also include induced sputum sampling pre-dose and post-dose. The subject will be discharged after dosing or sputum sampling as applicable, providing there are no safety concerns. In the event of BID dosing; on Days 4 to 9 the subjects will be required to attend the unit for the evening dose (i.e. return in the evening on Day 4 and attend twice daily on Days 5 to 9) and will be discharged after dosing, providing there are no safety concerns. The subjects will then return to the clinical unit on the morning of Day 10 where they will then remain resident overnight until Day 11 (24 hours after the last dose). After completion of safety assessments, they will be discharged providing there are no safety concerns. They will return to the clinic on Days 14 and 17 for collection of PK blood samples (Day 14 only) and safety evaluations. A safety follow-up telephone call will be performed 11 to 17 days after the last dose to check the status of unresolved AEs and to record any new AEs that have occurred after the last visit as well as any changes to concomitant medications. **Part 3 (Crossover)** Part 3 is a 2-period, randomised, crossover study to assess the safety, tolerability and PK of single doses of ZP-059 compared to single doses of oral voriconazole in 16 male and female subjects with physician confirmed documented diagnosis of mild to moderate stable asthma. The dose of ZP-059 will be confirmed after completion of SAD cohorts 1 to 4 and review of the available safety data. Hence, dosing of Part 3 may occur prior to/ in parallel with dosing in Part 2. Eligible subjects will be randomised to receive a single dose of ZP-059 via DPI or a single oral dose of voriconazole in Period 1. Each subject then will receive the alternative treatment in Period 2 such that on completion of the study, all subjects will have received a single dose of ZP-059 via DPI and a single oral dose of 200

	mg voriconazole (VFEND®). The actual dose of ZP-059 will be determined at the safety review performed after completion of cohorts 1 to 4 (SAD) and will not exceed the highest dose used in Part 1. Dosing intervals between subjects in Part 3 are not deemed necessary, however may be implemented at the discretion of the investigator (in consultation with the sponsor, if required). Subjects should be dosed at approximately the same time of day in each study period. Subjects will be required to fast (water permitted) for at least 1 hour prior to each dose and 1 hour post each dose. The washout period between doses in each treatment period (TP), (i.e. TP1 Day 1 dose to TP2 Day 1 dose) will be a minimum of 96 hours. Subjects will undergo safety, tolerability and PK evaluations at specified time points during the study. They will remain resident in the clinic until Day 6. They will be discharged from the unit after completion of Treatment Period 2 assessments up to 24 hours post-dose and providing there are no safety concerns,. Subjects will return to the clinic on Days 7 and 9 for collection of 48 hour and 96 hour post dose (Treatment Period 2) PK blood and induced sputum samples (Day 7 only), and for safety evaluations to be completed. A safety follow-up telephone call will be performed 8 to 12 days after last dose (Period 2) to check the status of unresolved AEs and to record any new AEs that have occurred after the last visit as well as any changes to concomitant medications. Sputum producer stratum (minimum of 6 subjects): It is planned that a minimum of 6 out of the 16 subjects to be randomised in Part 3 will provide sufficient sputum samples at screening as per inclusion criteria 13. All subjects in Part 3 will however attempt to provide a sputum sample at the indicated timepoints as detailed in the study schedule of activities (SOA) in Section 1.2.3 (Part 3), regardless of whether they produce an adequate sample at screening.
Number of subjects	Part 1 (SAD): 24 healthy subjects (4 cohorts of 6 subjects) and an optional additional cohort of 6 subjects. Part 2 (MAD): 18 subjects with mild stable asthma (3 cohorts of 6 subjects) and up to 2 optional additional cohorts of 6 subjects. Part 3 (Crossover): 16 subjects with mild to moderate stable asthma. Subjects who discontinue the study may be replaced at the discretion of the Sponsor.
Duration of the study	Part 1 (SAD, healthy subjects): Subjects will receive a single dose of ZP-059 on 1 occasion. The estimated time from screening to the end of the study for each subject is approximately 6 weeks. Part 2 (MAD, mild, stable asthma subjects): Subjects will either receive a single dose of ZP-059 on Days 1 to 10 (total of 10 doses) or will receive twice daily doses of ZP-059 on Days 1 to 9 and one dose of ZP-059 on the morning of Day 10 (total

	19 doses). The estimated time from screening to the end of the study for each subject is approximately 8 weeks. Part 3 (Crossover, mild to moderate, stable asthma subjects): Subjects will receive a single dose of IMP on 2 occasions. The estimated time from screening to the end of the study for each subject is approximately 7 weeks.
Interim data reviews	The data reviews will be conducted by the safety advisory committee (SAC), which will comprise the Principal Investigator (or delegate) and the sponsor's medical monitor as a minimum. Additional data available at the time of each scheduled meeting may also be reviewed. **Part 1 (SAD)** There will be an interim data review before each dose escalation to the next dose level to determine safety and tolerability. The time between cohorts will be sufficient to allow this review. Interim reviews will be based on safety data from a minimum of 4 dosed subjects who have completed up to a minimum of 24 hours post-dose for each dose level. Progression to the next dose level will only occur after a review of safety data from the previous dose level confirms that it is safe to do so. The interim decision meeting following SAD cohort 2 will also determine the dose to be administered in Part 2 MAD cohort 1. Based on the observed data, it may be necessary or desirable to administer a previously administered dose, a reduced dose or a dose level higher than planned (as an additional cohort of 6 subjects) in order to determine the safe starting dose for Part 2. A repeat dose level or higher dose level will only be assessed provided no dose escalation or study stopping criteria have been met. Single doses will not exceed 40 mg of ZP-059 based on safety margins calculated following non-clinical studies. For each dose escalation, the dose increase will not be more than 3-fold. **Part 2 (MAD)** There will be an interim data review before each dose escalation to the next dose level to determine safety and tolerability. The time between cohorts will be sufficient to allow this review. There will be an interim data review after completion of MAD cohort 1 and SAD cohort 3 to confirm the dose level to be administered in MAD cohort 2 and after completion of MAD cohort 2 and SAD cohort 4 to confirm the dose level to be administered in MAD cohort 3. The dose to be administered in MAD cohort 2 and in MAD cohort 3 will not exceed the highest dose investigated in the previous SAD cohorts. The interim review will be based on safety data from a minimum of 4 dosed subjects who have completed up to a minimum of 24 hours after dosing on Day 10 from MAD cohort 1 and MAD cohort 2 respectively and up to a minimum of 24 hours post-dose from SAD cohort 3 and SAD cohort 4 respectively. Progression to MAD cohort 2 and MAD cohort 3 respectively will only occur after a review of safety data confirms that it is safe to do so.

	Up to 2 optional additional cohorts of 6 subjects (Cohort 4 and Cohort 5) may be enrolled in Part 2 if it is deemed appropriate to repeat a dose level, assess an additional dose level than planned or assess a different dosing regimen, however, the dose will not exceed the highest dose studied in Part 1.
Pharmacokinetic Assessments	For each study part, the serum concentration data for voriconazole and N-oxide voriconazole will be analysed using PKNCA (version 0.8.1 or higher) with R (version 3.2.2 or higher). The following non-compartmental PK parameters of voriconazole and N-oxide voriconazole will be calculated to obtain estimates of the following single dose PK parameters (where possible and appropriate): Parts 1, 2 and 3 (in Part 3, Day 1 of TP1 and Day 1 of TP2): AUC_{0-t}, AUC_{0-inf}, AUC_{tau}, C_{max}, t_{max}, K_{el}, $t_{1/2}$, CL/F and Vz/F, where AUC_{0-t} is: • AUC_{0-12} for Part 1, AUC_{0-24} for Part 2 and AUC_{0-96} for Part 3 AUC_{0-t}, AUC_{0-inf} and C_{max} for Part 3 will also be derived based on the Part 1 PK and separately the Part 2 PK time points, so that a like-for-like comparison between Part 3 and Part 1 and between Part 3 and Part 2 can be performed for these PK parameters. Part 2 (Day 10): AUC_{0-tau}, $C_{max,ss}$, $t_{max,ss}$, C_{min}, C_{trough}, $C_{ss,av}$, %fluctuation and %swing (as appropriate and when applicable). PK parameters will be derived in addition to those detailed for Day 1. Accumulation ratios will be calculated from Day 1 and Day 10 AUC_{0-tau} and C_{max} values, and the linearity ratios will be calculated from the ratio of the Day 10 AUC_{tau} and Day 1 AUC_{0-inf}. Metabolite ratios (as appropriate) will be calculated for AUC and C_{max} parameters. Additional PK parameters may be calculated if deemed appropriate.
Investigational medicinal product, dose and mode of administration	Test IMP: Dry powder for oral inhalation with a formulation comprising voriconazole as the active ingredient; Edry-Voriconazole 5 mg capsule **ZP-059** Reference IMP (Part 3): VFEND® oral film-coated tablet (200mg); a currently marketed oral voriconazole formulation by Pfizer Limited, UK Dry Powder Inhaler for administration of voriconazole capsules: RS01 inhaler (RS01 Monodose inhaler, product code 239700004AA) **Table 1 Investigational Medicinal Products**

Study Part	Cohort	IMP	Dose and Route of Administration

	1	SAD 1	ZP-059	5 mg (1 x 5 mg capsule) ZP-059 [a] Administered via DPI on Day 1
		SAD 2	ZP-059	ZP-059 (Dose TBD) Administered via DPI on Day 1
		SAD 3	ZP-059	ZP-059 (Dose TBD) Administered via DPI on Day 1
		SAD 4	ZP-059	ZP-059 (Dose TBD) Administered via DPI on Day 1
	2	MAD 1	ZP-059	ZP-059 (Dose TBD) Administered via DPI once daily on Days 1 to 10 or twice daily on Days 1 to 9 and once on Day 10
		MAD 2	ZP-059	ZP-059 (Dose TBD) Administered via DPI once daily on Days 1 to 10 or twice daily on Days 1 to 9 and once on Day 10
		MAD 3	ZP-059	ZP-059 (Dose TBD) Administered via DPI once daily on Days 1 to 10 or twice daily on Days 1 to 9 and once on Day 10
	Study Part	Treatment Period	IMP	Dose and Route of Administration
	3	1 or 2	ZP-059	ZP-059 (Dose TBD) Administered via DPI on Day 1 of Period 1 or Period 2
			Voriconazole (VFEND®) oral film-coated tablet	200 mg Voriconazole (VFEND® - oral film-coated tablet) on Day 1 of Period 1 or Period 2
	[a] Fixed starting dose DPI; dry powder inhaler TBD; to be determined Each capsule delivers 5 mg of voriconazole			
Safety assessments	Adverse events Clinical chemistry, haematology and urinalysis SARS-COV-2 testing Vital signs (blood pressure, pulse rate, respiratory rate, temperature) Electrocardiogram Pulse oximetry Spirometry Physical examination			
Statistical methodology	No formal statistical analysis will be performed for safety data. For PK data: Part 1 and Part 2:			

	Formal statistical analysis will be performed on the PK parameters $AUC_{(0\text{-}t)}$, , $AUC_{(0\text{-}inf)}$ and C_{max} to assess dose proportionality using a power model approach, where t is 12 hours for Part 1 and 24 hours for Part 2. This analysis will be performed for the following: Part 1 (SAD): Day 1 Part 2 (MAD): Day 1 and Day 10 separately (assuming 3 or more dose levels are used). Part 3: Formal statistical analysis will be performed on the above PK parameters to assess relative bioavailability of ZP-059 to voriconazole. The PK parameters will undergo a natural logarithmic (log_e) transformation and will be analysed using a mixed effects ANOVA. The mixed effects ANOVA model will include fixed effect terms for treatment, period, sequence and sex and a random effect term for subject (nested within sequence). Adjusted geometric mean ratio (GMR) and 90% confidence intervals (CIs) for the adjusted GMR for the comparison between test ZP-059 and reference oral voriconazole tablets will be provided, where the ratio is defined as test/reference. In addition, the above PK parameters 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 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 subjects/Part 2 subjects, depending on the comparison.
Sample size calculation:	<u>Part 1 (SAD - Healthy Subjects) and Part 2 (MAD – Mild, Stable Asthma Subjects):</u> 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 an additional 6 subjects in 2 optional cohorts i.e. an additional 12 subjects in total) in Part 2 was chosen to minimise exposure to ZP-059 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. <u>Part 3 (Mild to Moderate, Stable Asthma Subjects):</u> 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 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.

1.2. Schedule of Activities (SoA)

1.2.1. Schedule of Activities for Part 1 (SAD)

Study Day	**-28 to -1**	**-1**	**1**													**2**	**3**	**5**	**8 to 12 days after dosing**	**Early Discontinuation Visit (EDV)**
					Times After Dosing (hours)												**Phone Call**	**Return Visit [a]**	**Follow-up Phone Call**	
Study Procedures [b]	**Screen**	**Adm**	**Pre-dose**	**0**	**0.25**	**0.5**	**0.75**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**				
Informed Consent	X																			
Medical History (including demographics)	X																			
Weight and Height [c]	X		X																	
Vein Assessment	X																			
Urine Drug Screen (including Cotinine)	X	X																		
Alcohol Breath Test	X	X																		
Serum Pregnancy Test [d]	X																			
Urine Pregnancy Test [d]			X															X		X
Inhaler Device Training	X		X																	
IMP Administration				X																
Discharge from the Clinic																X [e]				
Physical Examination [f]	X	X	X	◄												►		X		X
Safety Labs [g]	X															X		X		X
Serology (HIV/Hepatitis screen)	X																			

Study Day	**-28 to -1**	**-1**	**1**													**2**	**3**	**5**	**8 to 12 days after dosing**	**Early Discontinuation Visit (EDV)**
					Times After Dosing (hours)												**Phone Call**	**Return Visit [a]**	**Follow-up Phone Call**	
Study Procedures [b]	**Screen**	**Adm**	**Pre-dose**	**0**	**0.25**	**0.5**	**0.75**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**24**				
FSH (postmenopausal females only; if required)	X																			
Electrocardiogram [h]	X		X						X		X					X		X		X
Vital Signs [i]	X		X			X			X		X		X	X		X		X		X
Pulse Oximetry	X		X			X			X		X		X	X		X		X		X
Spirometry	X		X			X			X		X		X			X				
Adverse Events	◄																			►
Concomitant Medication	◄																			►
Blood Samples for PK assessments			X					X	X	X	X			X						

Part 1 Footnotes

ADM - admission

EDV – Early Discontinuation Visit

a. Subjects will return on Day 5 for safety evaluations.
b. Screening procedures (including informed consent) can be performed over more than 1 day. Repeat of study procedures is permitted on the day and/or on another day (as appropriate) at the discretion of the investigator.
c. Height and Weight at screening. Weight only on Day 1 (pre-dose).
d. All female subjects.
e. Discharge from clinic after completion of 24 hour post-dose assessments.
f. Full physical examination at screening, Day 5 and EDV. Symptom directed examination; if required at any other visits or times at the discretion of the investigator.
g. Clinical safety laboratory samples (clinical chemistry, haematology and urinalysis) must be performed within 7 days of Day 1; if this interval is exceeded, sampling must be repeated. Samples for clinical chemistry will be obtained following a fast of at least 8 hours (water permitted).
h. Performed in triplicate. For assessment of time windows, the time of the first ECG of the triplicate will be used.
i. Systolic and diastolic blood pressure, pulse rate and respiratory rate. Tympanic temperature measured at screening and pre-dose only.

Permitted windows for all relevant procedures and dosing will be provided in the Study Reference Manual. Where the protocol requires more than one procedure to be completed at the same time point, all efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Any other procedures scheduled at the same time point will be performed either before or after the PK, as appropriate.

1.2.2. Schedule of Activities for Part 2 (MAD – Mild Asthmatics)

Study Day	**-28 to -1**	**-4/-3[bb]**	**-1**	**Treatment Period**												**Return Visits [a]**		**Follow-up Phone Call**	**EDV**
				1			**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**14**	**17**	**11 to 17 days after last dose**	
Study Procedures [b]	**Screening**		**Adm**	**Pre-dose**	**0**	**Post-dose**														
Residential Period			◄———						——►						◄——►					
Informed Consent	X																			
Medical History (including demographics)	X																			
Weight and Height [c]	X			X																
Vein Assessment	X																			
Urine Drug Screen (including Cotinine)	X		X																	
Alcohol Breath Test	X		X																	
Serum Pregnancy Test [d]	X																			
Urine Pregnancy Test [d]				X														X		X
Inhaler Device Training	X[cc]			X																
Discharge from the Clinic [e]									X							X				
Physical Examination [f]	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Safety Labs [g]	X						X[h]					X[i]				X[j]		X		X
Serology (HIV/Hepatitis screen)	X																			
FSH (postmenopausal females only; if required)	X																			
SARS-CoV-2 Test[aa]		X																		
Electrocardiogram [k]	X			X		X[l]	X[h]			X[i]					X[m]			X		X
Vital Signs [n]	X			X		X[o]	X[h]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[p]	X[j]	X	X		X
Tympanic Body Temperature	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X		X
Pulse Oximetry	X			X		X[o]	X[h]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[p]	X[j]		X		X
Spirometry [q]	X			X		X[r]	X[h]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[s]	X[j]	X	X		X
Adverse Events	◄———																			——►
Concomitant Medications	◄———																			——►

Study Day	**-28 to -1**	**-4/-3[bb]**	**-1**	**Treatment Period**												**Return Visits [a]**		**Follow-up Phone Call**	**EDV**
				1			**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**14**	**17**	**11 to 17 days after last dose**	
Study Procedures [b]	**Screening**		**Adm**	**Pre-dose**	**0**	**Post-dose**														
IMP Administration [t]					X		X	X	X	X	X	X	X	X	X					
Blood Samples for PK assessments				X		X[u]	X[v]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[w]	X[j]	X			X[y]
Induced Sputum Samples for PK assessments												X								X[z]

ADM - admission

Part 2 Footnotes

EDV – Early Discontinuation Visit

a. Subjects will return on Day 14 and Day 17 for PK sample collection (Day 14 only) and safety evaluations.
b. Screening procedures (including informed consent) can be performed over more than 1 day. Repeat of study procedures is permitted on the day and/or on another day (as appropriate) at the discretion of the investigator. In the event of BID dosing; assessments will be performed relative to the 0-hour dose only.
c. Height and Weight at screening. Weight only on Day 1 (pre 0-hour dose).
d. All female subjects.
e. Residential Periods: Discharge from clinic after completion of Day 4 and Day 11 assessments as applicable.
f. Full physical examination at screening, Day 17 and EDV. Symptom directed examination; if required at any other visits or times at the discretion of the investigator.
g. Clinical safety laboratory samples (clinical chemistry, haematology and urinalysis) must be performed within 7 days of Day 1; if this interval is exceeded, sampling must be repeated. Samples for clinical chemistry will be obtained following a fast of at least 8 hours (water permitted).
h. 24 hours post 0-hour dose Day 1 and prior to Day 2, 0-hour dose administration.
i. Prior to 0-hour dosing.
j. 24 hours post the 0-hour dose on Day 10.
k. Performed in triplicate. For assessment of time windows, the time of the first ECG of the triplicate will be used.
l. Performed at 2 and 4 hours post 0-hour dose.
m. Pre-dose (0-hour) and post 0-hour dose at 2 and 4 hours.
n. Systolic and diastolic blood pressure, pulse rate and respiratory rate.
o. Performed at 0.5, 2, 4, 8 and 12 hours post 0-hour dose. If dosing is BID, the 12-hour assessment will be performed before the evening (i.e. 12-hour) dose.

p. Pre-dose (0-hour) and post 0-hour dose at 0.5, 2, 4, 8 and 12 hours.
q. Pre- and post-bronchodilator (salbutamol) reversibility testing at screening. At all other visits and time-points, spirometry may be performed pre- or post-bronchodilator; i.e. there are no requirements for bronchodilator restrictions after the screening visit.
r. Performed at 0.5, 2, 4 and 8 hours post 0-hour dose.
s. Pre-dose (0-hour) and post 0-hour dose at 0.5, 2, 4 and 8 hours.
t. On Days 4 to 9 the subjects will be required to attend the unit for the evening for their 12-hour dose (i.e. return in the evening on Day 4 and attend twice daily on Days 5 to 9) if dosing is BID.
u. **PK blood samples**: at 1.5, 2, 3, 4 and 12 hours post 0-hour dose. If dosing is BID, the 12-hour sample will be collected before the evening (i.e. 12-hour) dose.
v. **PK blood sample:** at 24 hours post 0-hour dose Day 1 and prior to Day 2, 0-hour dose administration. If dosing is BID, the 24 hour sample can be taken anytime pre-dose on Day 2.
w. **PK blood samples**: Pre-dose (0 hour) and post 0-hour dose at 1.5, 2, 3, 4 and 12 hours.
x. **Induced Sputum Samples for PK assessments**: Pre-dose (0 hour) and post 0-hour dose at 3 hours and 6 hours.
y. **PK blood sample:** Only required if EDV is performed up to and including Day 14.
z. **Induced Sputum Samples for PK assessments:** Only required if EDV is performed up to and including Day 7.
aa. Subjects will undergo a SARS-COV-2 RT-PCR test. Subjects testing negative may proceed to enrol in the study, provided other eligibility criteria are met; Subjects who test positive should be withdrawn from screening for the study and undergo or be referred for appropriate medical care as determined by local policy for managing a positive result. SARS-COV-2 RT-PCR test may be conducted at any time between Day -4 and Day -3 at the discretion of the site. Additional RT-PCR testing may be performed throughout the study if deemed necessary by the investigator.
bb. Day -4/-3 procedures may be performed on the same day as the screening procedures if screening is performed within 3 or 4 days of dosing.
cc. Inhaler device training at screening is to be a demonstration only.

Permitted windows for all relevant procedures and dosing will be provided in the Study Reference Manual. Where the protocol requires more than one procedure to be completed at the same time point, all efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Any other procedures scheduled at the same time point will be performed either before or after the PK, as appropriate.

1.2.3. Schedule of Activities for Part 3 (Mild to Moderate Asthmatics)

1.2.3.1 Part 3 Schedule of activities: Screening to Day 4

			Treatment Period 1 [a]																
Study Day	**-28 to -1**	**-1**	**1**												**2**		**3**	**4**	
Treatment Days			**Day 1**												**Day 2**		**Day3**	**Day 4**	
					Times After Dosing (hours)															
Study Procedures [b]	**Screen**	**Adm**	**Pre-dose**	**0**	**0.25**	**0.5**	**0.75**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**23**	**24**	**48**	**72**
Residential Period		◄	►																
Informed Consent	X																		
Medical History (including demographics)	X																		
Weight and Height [c]	X		X																
Vein Assessment	X																		
Urine Drug Screen (including Cotinine)	X	X																	
Alcohol Breath Test	X	X																	
Serum Pregnancy Test [d]	X																		
Urine Pregnancy Test [d]			X																
Inhaler Device Training	X[n]		X [e]																
Randomisation			X																
IMP Administration				X															
Physical Examination [f]	X		X	◄													►	X	X

			Treatment Period 1 [a]																
Study Day	**-28 to -1**	**-1**	**1**													**2**	**3**	**4**	
Treatment Days			**Day 1**													**Day 2**	**Day3**	**Day 4**	
					Times After Dosing (hours)															
Study Procedures [b]	**Screen**	**Adm**	**Pre-dose**	**0**	**0.25**	**0.5**	**0.75**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**23**	**24**	**48**	**72**
Residential Period		←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Safety Labs [g]	X		X													X			
Serology (HIV/ Hepatitis screen)	X																		
FSH (postmenopausal females only; if required)	X																		
SARS-CoV-2 Test [m]	X																		
Electrocardiogram [h]	X		X			X			X		X					X			
Vital Signs [i]	X		X			X			X		X		X	X		X		X	
Tympanic Body Temperature	X		X													X		X	X
Pulse Oximetry	X		X			X			X		X		X	X		X		X	
Spirometry [j]	X		X			X			X		X		X			X		X	
Concomitant Medication	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Adverse Events	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→
Blood Samples for PK assessments			X		X		X	X	X	X	X	X	X	X	X		X	X		
Induced Sputum Samples for PK assessments [l]	X [l]								X			X				X		X		

Part 3 Footnotes

ADM - admission

a. Washout interval of a minimum of 96 hours between doses in each treatment period i.e. Day 1 dosing to Day 1 of the next treatment period. **Example of minimum washout period**: Period 1, Day 1 Monday the earliest Period 2, Day 1 of the next treatment period is the following Friday.
b. Screening procedures (including informed consent) can be performed over more than 1 day. Repeat of study procedures is permitted on the day and/or on another day (as appropriate) at the discretion of the investigator.
c. Height and Weight at screening. Weight only on Day 1 (pre-dose) of each treatment period.
d. All female subjects.
e. Of the relevant treatment period only, training will be performed pre-dose on Day 1.
f. Full physical examination at screening Study Day 5 and Study Day 9. Symptom directed examination; if required at any other visits or times at the discretion of the investigator.
g. Clinical safety laboratory samples (clinical chemistry, haematology and urinalysis) must be performed within 7 days of Day 1, Period 1; if this interval is exceeded, sampling must be repeated. There is no requirement for Day 1 pre-dose laboratory assessment results to be available before dosing in either Period 1 or Period 2. Samples for clinical chemistry will be obtained following a fast of at least 8 hours (water permitted).
h. Performed in triplicate. For assessment of time windows, the time of the first ECG of the triplicate will be used.
i. Systolic and diastolic blood pressure, pulse rate and respiratory rate.
j. Pre and post bronchodilator (salbutamol) reversibility testing at screening. At all other visits and time-points spirometry may be performed pre or post bronchodilator; i.e. there are no requirements for bronchodilator restrictions after the screening visit.
k. Screening sputum samples will be collected for assessment of eligibility only and will not be analysed.
l. A minimum of 6 out of the 16 subjects to be randomised in Part 3 must provide a sufficient sputum sample at screening as per inclusion criteria 13.
m. Subjects will undergo a SARS-COV-2 RT-PCR test prior to sputum induction at screening. Subjects testing negative may proceed to enrol in the study, provided other eligibility criteria are met; Subjects who test positive should be withdrawn from screening for the study and undergo or be referred for appropriate medical care as determined by local policy for managing a positive result. SARS-COV-2 RT-PCR test must be performed within 14 days of Day 1, Period 1. If this interval is exceeded, sampling must be repeated. Additional RT-PCR testing may be performed throughout the study if deemed necessary by the investigator.
n. Inhaler device training at screening is to be a demonstration only.

Permitted windows for all relevant procedures and dosing will be provided in the Study Reference Manual. Where the protocol requires more than one procedure to be completed at the same time point, all efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Any other procedures scheduled at the same time point will be performed either before or after the PK, as appropriate.

1.2.3.2 Part 3 Schedule of activities: Day 5 to EDV

	End of Treatment Period 1 / Treatment Period 2[a]																	Follow-Up Phone Call[b]	EDV[d]
Study Day	**5**													**6[c]**		**7[e]**	**9[e]**	**8 to 12 days after last dose**	
Treatment Day	**TP1 Day 5 /pre dose TP2**	**TP 2 - Day 1**												**Day 2**		**Day 3**	**Day 5**		
		Times After Dosing (hours)																	
Study Procedures	**96hr / Pre-dose [j]**	**0**	**0.25**	**0.5**	**0.75**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**16**	**23**	**24**	**48**	**96**		
Residential Period[c]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	→				
Weight	X																		
Urine Pregnancy Test [f]																	X		X
IMP Administration		X																	
Physical Examination [g]	X	←	—	—	—	—	—	—	—	—	—	—	—	—	—	→	X		X
Safety Labs[m]	X													X			X		X
Electrocardiogram [h]	X			X			X		X					X			X		X
Vital Signs [i]	X			X			X		X		X	X		X		X	X		X
Tympanic Body Temperature	X													X		X	X		X
Pulse Oximetry	X			X			X		X		X	X		X		X	X		X
Inhaler Device Training	X [k]																		
Spirometry	X			X			X		X		X			X		X	X		X
Concomitant Medication	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→		
Adverse Events	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→		
Blood Samples for PK assessments	X		X		X	X	X	X	X	X	X	X	X		X	X	X		X
Induced Sputum							X			X				X		X			

Samples for PK assessments [l]																			

Part 3 Footnotes

a. Washout interval of a minimum of 96 hours between doses in each treatment period i.e. Day 1 dosing to Day 1 of the next treatment period. **Example of minimum washout period**: Period 1, Day 1 Monday the earliest Period 2, Day 1 of the next treatment period is the following Friday.
b. Follow-up Phone Call 8 to 12 days after last dose in Period 2, or in the event of early discontinuation to be performed after last dose in Period 1.
c. Discharge from clinic after completion of treatment period 2, 24-hour post-dose assessments.
d. The EDV is only to be performed for subjects who discontinue during a treatment period (prior to Study Day 5 or Study Day 9) i.e. is not required if discontinue during the washout period.
e. Subjects will return on Day 7 and Day 9 for collection of PK blood sample, induced sputum sample (Day 7 only) and safety evaluations.
f. All female subjects.
g. Full physical examination at screening, Study Day 5 and Study Day 9. Symptom directed examination; if required at any other visits or times at the discretion of the investigator.
h. Performed in triplicate. For assessment of time windows, the time of the first ECG of the triplicate will be used.
i. Systolic and diastolic blood pressure, pulse rate and respiratory rate.
j. All +96-hour procedures for Treatment Period 1 are to be performed prior to Treatment Period 2 dosing and can also be considered as Treatment Period 2 pre dose assessments.
k. Of the relevant treatment period only, training will be performed pre-dose on Day 1.
l. A minimum of 6 out of the 16 subjects to be randomised in Part 3 must provide a sufficient sputum sample at screening as per inclusion criteria 13.
m. Clinical safety laboratory samples (clinical chemistry, haematology and urinalysis), Samples for clinical chemistry will be obtained following a fast of at least 8 hours (water permitted).

2. Introduction

Asthma is a chronic condition which occurs as a result of immune response in the bronchial airways, causing intermittent inflammation and airway swelling. Many factors, including infection as well as different allergens can irritate and inflame the airways, leading to worsening of asthma symptoms.

The frequency of *Aspergillus* sensitisation in asthmatic subjects varies, with a range from 16% to 38% being reported in different geographical regions [1]. Some asthmatics with sensitisation to *Aspergillus* present with allergic bronchopulmonary aspergillosis (ABPA), a progressive fungal allergic lung disease, which can be a cause of poorly controlled asthma. While ABPA is often under-diagnosed due to the complexity and relative lack of standardisation of diagnostic criteria, prevalence of ABPA in asthmatics of up to 12.9% has been reported [2, 3].

The link between asthma severity and fungal allergy is well established. Indeed, sensitisation to fungal allergens and ABPA are associated with the risk of severe asthma exacerbations requiring multiple hospital and intensive care admission [4, 5] and management with prolonged courses of systemic corticosteroids and azoles [6], which are associated with significant adverse effects.

In this setting, there is a need for development of new, effective and well tolerated therapies to control fungus-associated inflammation of the airways. Inhaled administration of antifungals like voriconazole could potentially be an effective alternative treatment option for ABPA and may improve asthma control and reduce its severity and frequency of exacerbations.

2.1. Study Rationale

There is a growing evidence linking asthma severity with fungal allergy. Sensitisation to fungi and long-term or uncontrolled fungal infection are associated with poor control of asthma.

Several studies of antifungal treatments in asthmatic patients with ABPA showed improvement in patient quality of life, reduction in the frequency of exacerbations and corticosteroid requirements [7, 8]. Anti-fungal treatment of ABPA is based on various agents from the azole class, like itraconazole, voriconazole or posaconazole [9]. These medications have shown to be beneficial against *Aspergillus* spp. colonisation of the airways.

Randomised controlled trials reported that treatment with oral itraconazole for 4 months improved both clinical outcomes and reduce inflammation in asthmatics with ABPA [10, 11, 12].

The major problem with the use of itraconazole is the high failure rate and frequent adverse events (AEs). The most common side effects include nausea and vomiting, diarrhea and flatulence, constipation, hyperlipidemia, hypokalemia, liver enzyme elevations, peripheral edema, and peripheral neuropathy. Perhaps most importantly, adrenal suppression, especially when combined with some inhaled corticosteroids (ICS), can occur in many patients. Occasionally, itraconazole has been associated with heart failure [13].

Oral itraconazole is also associated with variable pharmacokinetics (PK). The oral bioavailability of itraconazole in healthy volunteers can be low and dependent on food intake, and may be further reduced in patients with poor digestive function [14].

Newer oral triazoles with excellent anti-A*spergillus* activity (voriconazole and posaconazole) have also been reported as beneficial in the treatment of ABPA [14]. Chishimba et al [15] reported high clinical response rates to both voriconazole and posaconazole in patients who discontinued treatment with itraconazole either due to lack of efficacy or adverse events. Clinical responses were associated with a marked reduction in oral corticosteroids and short-acting beta-agonist use, health-care utilization due to asthma, and improvement in overall health status.

Voriconazole has a similar in vitro minimum inhibitory concentration against *A. fumigatus* as itraconazole and posaconazole, and an improved safety and PK profile, with good penetration into the lung tissue and epithelial lining fluid [16].

However, despite promising efficacy in ABPA patients and the improved PK profile, systemic, prolonged use of voriconazole is still associated with a significant number of adverse events and treatment discontinuations, with visual toxicity being one of the main reasons for poor patient tolerability [17]. Development of an inhaled formulation of voriconazole could offer an attractive therapeutic alternative, deprived of the side effects associated with systemic exposure.

ZP-059 (inhaled voriconazole) is an anti-fungal product being developed as a therapeutic for the treatment of ABPA in patients with asthma and cystic fibrosis (CF).

This study will evaluate the safety, tolerability and PK of single and multiple ascending doses of ZP-059 capsules administered as dry powder for inhalation in Part 1 to healthy volunteers (single ascending dose; SAD) and in Part 2 to subjects with mild asthma (multiple ascending dose; MAD), respectively.

In Part 3, the bioavailability of ZP-059 in subjects with mild to moderate stable asthma will be compared to that of oral voriconazole. Part 3 will only start after review of safety data from cohorts 1 to 4 of Part 1 (SAD) have been completed.

Parts 2 and 3 of the study will also explore voriconazole concentrations in induced sputum samples in asthmatic subjects.

As part of the safety and tolerability assessment, this study will investigate the effects of ZP-059 on airway function in both mild and mild to moderate stable asthma subjects.

Population rationale:

ABPA affects both men and women; therefore, a target population of both male and non-pregnant, non-lactating female subjects of childbearing potential (providing they agree to use highly effective contraception) or women of non-childbearing potential between 18 and 60 years will be suitable for all parts of the study (i.e. Parts 1, 2 and 3). As PK of voriconazole has been shown to differ between males and females, in all parts of the study (i.e. Parts 1, 2 and 3) every effort will be made to include as close as possible an equal balance between male and female subjects; in Part 1 and Part 2 this will be in each of the individual cohorts.

Japanese and Chinese subjects will not be included in this study as voriconazole exposures in these populations could be influenced by poor metabolism due to CYP2C19 genotype [18].

2.2. Background

Aspergillus fumigatus is a mould that can cause invasive, life threatening infections, predominantly in immunocompromised patients. At the same time, airway colonization with *A. fumigatus* in patients with chronic lung disease such as asthma and CF may lead to an allergic immune response without tissue invasion, resulting in a complex manifestation of clinical symptoms and radiological and laboratory test abnormalities.

The immunological response to fungal antigens in the airway that leads to the development of ABPA results in T-helper type 2 (Th2) cell activation and inflammatory cell recruitment to the airways, the most significant of which are eosinophils. Expression of interleukin-4 and interleukin-5 (IL-4 and IL-5) is central to these processes. IL-4 stimulates the upregulation of adhesion molecules involved in eosinophil recruitment and the production of IgE by B cells, which in turn leads to mast cell activation. IL-5 produced by both Th2 cells and mast cells is a key mediator of eosinophil activation. Activation of both mast cells and eosinophils results in the release of mediators that induce bronchoconstriction [19, 20].

The main symptoms of ABPA are those of poor controlled asthma with wheeze, dyspnea, mucus production, bronchoconstriction and productive cough. Repeated episodes of mucus production, bronchial obstruction and inflammation can lead to the development of bronchiectasis that may progress to fibrosis if untreated. The clinical symptomatology is associated with increased levels of total and *Aspergillus*-specific IgE, positive

immediate hypersensitivity skin test for *Aspergillus,* peripheral eosinophilia, serum precipitins or *Aspergillus*-specific IgG, and radiographic pulmonary opacities, either transient (consolidation, nodules, or finger-in-glove) or permanent (bronchiectasis or fibrosis) [20, 21].

Hence, recognition and proper management of ABPA is very important in order to prevent permanent lung damage in patients with severe, difficult to control asthma. Long-term treatment of ABPA aims to control inflammation and prevent further injury to the lungs. Use of oral corticosteroids and antifungals are the main stay of treatment to reduce the number of exacerbations. However, new treatment modalities are required to improve tolerability of therapy and also to reduce the need for systemic steroids.

2.3. Benefit/Risk Assessment

Allergic bronchopulmonary aspergillosis (ABPA) is a rare disease that affects patients with asthma and cystic fibrosis (CF). There is currently no specific therapy for treatment of ABPA in asthmatics and this debilitating condition has led researchers to find new avenues of treatments, including new ways of administering antifungals. Oral antifungals like voriconazole are useful for ABPA along with steroids as they have shown to improve clinical symptoms and lung function, reduce frequency of exacerbations, and to provide steroid-sparing effect. However, the confidence in the beneficial effects of oral voriconazole is limited by poor PK and adverse events in high concentrations. Hence, an inhaled formulation of voriconazole by using Edry technology, can overcome these limitations with efficient lung deposition, resulting in a lower systemic exposure and subsequently minimizing toxic effects.

Given the dynamic, ongoing global health crisis related to COVID-19, the risk to subjects must be assessed and addressed on an ongoing basis. Risk mitigation elements include a reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 that will be conducted at Day -4/-3 for Part 2 and prior to screening sputum induction for Part 3. While subjects are resident in the clinic, the clinic staff will follow locally established risk mitigation processes to minimize exposure to SARS-COV-2 for subjects and staff. Any subjects testing positive for SARS-COV-2 during the study will receive the appropriate medical care, and precautions, according to local requirement, will be taken to ensure the safety of other subjects and research staff. Any additional policies or information will be assessed on an ongoing basis and integrated into study conduct, as appropriate.

2.3.1. Risk Assessment

In the population selected for this study, ZP-059 and all study related procedures do not pose any significant risks because pre-clinical studies have shown that systemic exposure of ZP-059 is low (IB section 5.3.1) and all staff are competent in the study related procedures.

VFEND® is a licensed broad-spectrum, antifungal agent (Ref: https://bnf.nice.org.uk/drug/voriconazole.html, https://www.medicines.org.uk/emc/product/7383/smpc

Generally, asthmatics are considered vulnerable when compared to a healthy population, However, the asthmatic population included in part 2 and part 3 of the study are mild (Part 2) or mild to moderate (Part 3) and stable with no other significant co-morbidities.

2.3.2. ZP-059

ZP-059 is an antifungal product, being developed using Edry technology as an inhaled therapy, for the treatment of ABPA in patients with asthma. It has been developed such that there is efficient lung deposition, compared to other inhalative treatments, avoiding extra pulmonary deposition, and causing a low systemic exposure level, as well regarding effects on plasma concentration of contraceptives.

The overall summary of toxicology data for ZP-059 is provided in the Investigator's Brochure (IB). There was no evidence of systemic toxicity in the preclinical studies. All the repeat doses were tolerated well apart from a single episode of vomiting and reduction in food consumption in dog at 35.7mg/kg/day. Based on animal data the no-observed-adverse-affect-level (NOAEL) was 49.3mg/kg/day in rats and 21mg/kg/day in dogs and in our study the starting dose is considerably lower.

2.3.3. Induced Bronchoconstriction

Bronchoconstriction is an expected adverse reaction with any inhaled therapy and is a theoretical risk for ZP-059. Subjects will be monitored for AEs and for bronchoconstriction (through scheduled spirometry assessments) throughout the study and treated with bronchodilators e.g. salbutamol and other appropriate therapies as deemed necessary by the Investigator, if required for symptomatic bronchoconstriction.

2.3.4. Oral voriconazole

VFEND®, is a licensed broad-spectrum, triazole antifungal agent which is indicated in adults and children aged 2 years and above for the treatment of invasive aspergillosis, candidemia in non-neutropenic patients etc. It is available as a lyophilized powder for solution for intravenous infusion, film-coated tablets for oral administration, and as a powder for oral suspension.

Repeat dose toxicity studies of oral voriconazole indicated hepatoxicity occurs at plasma exposures similar to those obtained at therapeutic doses in humans. Animal data has also shown minimal adrenal changes. Regular safety assessments, including laboratory

tests, vital signs, physical examination, ECGs as per the schedule of activities will be performed throughout the study.

Voriconazole has shown teratogenic effects in rats and embryotoxic effects in rabbits with no observed impairment of male or female fertility in rats. Overall, there was no special hazard seen for humans. Contraceptive measures will be followed as per protocol. Due to being substrates for CYP3A4, the plasma concentration of hormonal contraceptives may increase by concomitant administration of voriconazole. However, the inhaled dose has low systemic exposure and there is only a single oral dose of voriconazole administered in part 3, with no increased risk to women of childbearing potential on hormonal contraceptives. Strong CYP3A4 inhibitors and inducers as concomitant medication will not be permitted for the duration of the study.

2.3.5. Other

During cannulation, more than one attempt may be needed to insert the cannula in a vein of a subject and it is possible that bruising and/or inflammation may be experienced at the site of cannulation. More rarely fainting, a local clot developing or local infection can occur. At times when a cannula is not required, blood samples will be taken via venepuncture. This can also result in discomfort, bruising or a haematoma at the site of puncture.

Electrocardiogram stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

Sputum induction is a relatively non-invasive method to obtain sputum for analysis in clinical practice and in research. It is performed using an aerosol of normal and hypertonic saline generated by an ultrasonic nebuliser. Subjects will be pre-treated with a bronchodilator, e.g. 200 to 400 µg of salbutamol will be administered via a spacer device as required to mitigate against aerosol induced bronchoconstriction. Subjects will be monitored during the procedure (by performing regular lung function), which will be stopped if the subject develops symptoms suggestive of bronchoconstriction or a significant fall (i.e. ≥ 20%) in forced expiratory volume in 1 sec (FEV_1), and treated with a bronchodilator as appropriate. Site-specific standard operating procedures (SOPs) for sputum induction will be followed.

All other investigations such as measurements of blood pressure and pulse rate are well established methods which do not present a risk to the subjects.

2.3.6. Benefit Assessment

There is no benefit to the subjects from taking part in this study. The development of a product to improve the treatment of ABPA in patients with severe asthma or CF will be of benefit to the wider community/patients with this condition.

2.3.7. Overall Benefit: Risk Conclusion

The administered doses will be gradually escalated following defined procedures to guarantee the included participant`s appropriate safety. Hence, the overall benefit risk assessment is considered to be acceptable for the proposed trial based on the available pharmacological data from IB.

This trial will be conducted in compliance with the Declaration of Helsinki (1964 and amendments) current ICH E6 Good Clinical Practices and all other applicable local laws and regulations [24].

3. Objectives and Endpoints

3.1. Objectives

3.1.1. Primary Safety Objectives

Part 1:
To determine the safety and tolerability of single doses of ZP-059 in healthy subjects.

Part 2:
To determine the safety and tolerability of multiple doses of ZP-059 in subjects with mild stable asthma.

Part 3:
To determine the safety and tolerability of single doses of ZP-059 in subjects with mild to moderate stable asthma.

3.1.2. Pharmacokinetic (PK) Objectives

Part 1:
To characterize systemic PK of voriconazole after single doses of ZP-059 in healthy subjects.

Part 2:
To characterize systemic PK of voriconazole after multiple doses of ZP-059 in subjects with mild, stable asthma.

Part 3:
To characterize systemic PK of 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 (Parts 2 and 3 only)

Part 2:

To characterize 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 characterize voriconazole concentrations in induced sputum after single doses of ZP-059 and after single doses of oral voriconazole in subjects with mild to moderate stable asthma.

3.2. Endpoints

3.2.1. Safety Endpoints (Parts 1, 2 and 3)

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

3.2.2. Pharmacokinetic Endpoints (Parts 1, 2 and 3)

For each study part, the serum concentration data for voriconazole and N-oxide voriconazole will be analysed using PKNCA (version 0.8.1 or higher) with R (version 3.2.2 or higher).

For Parts 2 and 3, sputum concentration of voriconazole will be analysed.

Pharmacokinetic parameters:

The following non-compartmental PK parameters of voriconazole and N-oxide voriconazole will be calculated:

Parts 1, 2 and 3 (in Part 3, Day 1 of TP1 and Day 1 of TP2): AUC_{0-t}, AUC_{0-inf}, AUC_{tau}, C_{max}, t_{max}, K_{el}, $t_{1/2}$, CL/F and Vz/F, where AUC_{0-t} is:

- AUC_{0-12} for Part 1, AUC_{0-24} for Part 2 and AUC_{0-96} for Part 3

AUC_{0-t}, AUC_{0-inf} and C_{max} for Part 3 will also be derived based on the Part 1 PK and separately the Part 2 PK time points, so that a like-for-like comparison between Part 3 and Part 1 and between Part 3 and Part 2 can be performed for these PK parameters.

Part 2 (Day 10): AUC_{0-tau}, $C_{max,ss}$, $t_{max,ss}$, C_{min}, C_{trough}, $C_{ss,av}$, %fluctuation and %swing (as appropriate and when applicable). PK parameters will be derived in addition to those detailed for Day 1.

Accumulation ratios will be calculated from Day 1 and Day 10 AUC_{0-tau} and C_{max} values, and the linearity ratios will be calculated from the ratio of the Day 10 AUC_{tau} and Day 1 AUC_{0-inf}.

Metabolite ratios (as appropriate) will be calculated for AUC and C_{max} parameters.

Additional PK parameters may be calculated if deemed appropriate.

4. Study Design

4.1. Overall 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). In all parts of the study (i.e. Parts 1, 2 and 3) every effort will be made to include as close as possible an equal balance between male and female subjects; in Part 1 and Part 2 this will be in each of the individual cohorts.

Safety, tolerability and PK will be assessed following either single ascending (SAD) or multiple ascending (MAD) dosing of ZP-059 (Part 1 and Part 2, respectively).

Part 1 will comprise 4 separate cohorts (each containing 6 subjects) planned to receive single doses of ZP-059. The starting dose for Cohort 1 will be 5 mg with subsequent doses being determined from review of safety data by the SAC from the preceding cohorts. The criteria to be followed by the SAC are detailed in Section 6.6.4. The study will have an interleaved design.

Part 2 will comprise 3 separate cohorts (each containing 6 subjects) planned to receive daily doses of ZP-059 on Day 1 to 10. Dose levels for Part 2 will be determined from review of safety data by the SAC from Part 1. Part 2 cohort 1 will commence after a review of safety data from Part 1 cohort 2 confirms that it is safe to do so. The criteria to be followed by the SAC are detailed in Section 6.6.4

Part 3 is a 2-period, randomised crossover study in 16 subjects to assess the safety, tolerability and PK of single doses of ZP-059 and single doses of oral voriconazole. Part 3 will comprise of 1 cohort randomised to receive ZP-059 and 200 mg oral voriconazole; across 2 treatment periods with a minimum wash-out period of 96 hours.

The dose of ZP-059 for Part 3 will be confirmed after completion of SAD cohorts 1 to 4 and review of the available safety data. Hence, dosing of Part 3 may occur prior to/in parallel with dosing in Part 2.

Subjects will be screened for eligibility to participate in the study within 28 days before dosing (Day 1) For Part 2 subjects who completed the initial Screening Visit will attend the clinic on Day -4 or Day -3, for a SARS-COV-2 RT-PCR test. This may be performed on the same day as screening if screening is performed within 3 or 4 days of dosing. Subjects will then be admitted to the clinic on the evening of Day -1.

Further details of each study part are described in Sections 4.1.1 to 4.1.3.

4.1.1. Part 1 (SAD)

Part 1 is a single ascending dose (SAD) study to assess the safety, tolerability and PK of single doses of ZP-059 in 4 cohorts of healthy male and female subjects. Each cohort will comprise 6 subjects (planned total of 24 subjects). An evaluable subject for Part 1 (SAD) of the study is defined as a subject who has received a dose of ZP-059 and has sufficient data for evaluation of the safety and PK objectives as outlined in Section 3.1.1 and Section 3.1.2 – 3.1.3, respectively.

An additional cohort of 6 subjects (Cohort 5) may be enrolled if it is deemed appropriate to repeat a dose level, assess an interim dose level or assess a dose level higher than planned (Section 6.6.1). Single doses will not exceed 40 mg of ZP-059 based on safety margins calculated following non-clinical studies (Section 4.3). For each dose escalation, the dose increase will not be more than 3-fold. A repeat dose level or higher dose level will only be assessed provided no dose escalation or study stopping criteria have been met.

Eligible subjects will receive a single dose of ZP-059 on the morning of Day 1. Subjects will be required to fast (water permitted) for at least 1 hour prior to each dose and 1 hour post each dose.

ZP-059 is a first in human IMP and therefore an additional safety precaution has been considered for dosing in each cohort and dose level for Parts 1 and 2. For the first 2 subjects in each cohort, there will be a minimum interval of 20 minutes between dosing. After the second subject is dosed there will be at least a 30 minutes observation period before the remaining 4 subjects are dosed. The remaining subjects will be dosed if the first two subjects show no clinically significant safety or tolerability concerns (including vital signs measurements, spirometry, physical examinations (symptom directed if required) and review of any adverse events [AEs] including any acute side effects e.g. excessive coughing) at the discretion of the investigator. Any clinically significant findings from the first two subjects in the opinion of the investigator will be discussed with the Sponsor prior to dosing of the remaining 4 subjects. The dosing interval between dosing subjects in the remainder of the cohort will be at the discretion of the investigator (in consultation with the sponsor if required) i.e. this could be increased or decreased as appropriate.

The fixed starting dose for SAD Cohort 1 is 5 mg (1 x 5 mg capsule*) ZP-059 single dose administered via DPI (RS01 monodose device) on Day 1. *Capsule delivers 5 mg of voriconazole. Subsequent doses in the following cohorts will be determined from review of safety data from the preceding cohorts.

There will be an interim data review before each dose escalation to the next dose level to determine safety and tolerability. The time between cohorts will be sufficient to allow this review. Interim reviews will be based on safety data up to a minimum of 24 hours post-

dose for each dose level. Progression to the next dose level will only occur after a review of safety data from the previous dose level confirms that it is safe to do so. The interim decision meeting following SAD cohort 2 will also determine the dose to be administered in Part 2 MAD cohort 1. The data reviews will be conducted by the safety advisory committee (SAC), which will always comprise the Principal Investigator (or delegate) and the sponsor's medical monitor as a minimum (Section 6.6). Full details of interim data reviews, including dose escalation criteria, are provided in Sections 6.6.1 to 6.6.4.

Subjects will undergo safety, tolerability and PK evaluations at specified time points during the study (see Section 1.2). They will remain resident in the clinic until Day 2 after completion of safety assessments at 24 hours post-dose and providing there are no safety concerns, they will be discharged from the unit. A safety telephone call will be performed on Day 3 to check the status of unresolved AEs and to record any new AEs that have occurred after the last visit as well as any changes to concomitant medications. They will return to the clinic on Day 5 for safety evaluations to be performed. A safety follow-up call will be performed 8 to 12 days post dose to check the status of unresolved AEs and to record any new AEs that have occurred after the last visit as well as any changes to concomitant medications.

4.1.2. Part 2 (MAD)

Part 2 is a multiple ascending dose (MAD) study to assess the safety, tolerability and PK of multiple doses of ZP-059 in 3 cohorts of male and female subjects with a physician confirmed documented diagnosis of mild stable asthma. Each cohort will comprise 6 subjects (planned total of 18 subjects). An evaluable subject for Part 2 (MAD) of the study is defined as a subject who has received 10 days of dosing with ZP-059 and has sufficient data for evaluation of the objectives of the study.

Up to 2 optional additional cohorts of 6 subjects (Cohort 4 and Cohort 5) may be enrolled in Part 2 if it is deemed appropriate to repeat a dose level, assess an additional dose level or assess a different dosing regimen (), however, the dose will not exceed the highest dose studied in Part 1 (Section 6.6.2). If a selected dose does not provide the required data to meet the objectives of the study, a previously tested dose may be used in a subsequent cohort. However, if the dose level met the dose escalation or study stopping criteria, neither that dose level nor a higher dose will be repeated.

In each cohort, subjects will receive inhaled doses either once daily (QD) for 10 days or twice daily (BID) for 9 days and once in the morning of Day 10, as determined by the Sponsor based on data obtained in previous Part 1. In the event of QD dosing eligible subjects will receive QD doses of ZP-059 (at Hour 0) on Days 1 to 10. In the event of BID dosing, ZP-059 will be administered at Hours 0 and 12 on Days 1 to 9 and once in the morning of Day 10 (i.e. 19 doses in total). Subjects will be required to fast (water permitted) for at least 1 hour prior to each dose and 1 hour post each dose; in the event

of BID dosing this will be for both the 0 hour and the 12 hour doses. Following the first dose, subsequent doses will be administered within +/- 1 hour of the scheduled dosing time. If any of the additional cohorts (i.e. Cohorts 4 and 5) are required, subjects will receive either QD or BID doses, as may be appropriate.

For the first 2 subjects in each cohort, there will be a minimum interval of 20 minutes between dosing (Day 1; Hour 0). After the second subject is dosed there will be at least a 30 minutes observation period before the remaining 4 subjects are dosed (Day 1; Hour 0). The remaining subjects will be dosed if the first two subjects show no clinically significant safety or tolerability concerns (including vital signs measurements, spirometry, physical examinations (symptom directed if required) and review of any adverse events [AEs] including any acute side effects e.g. excessive coughing) at the discretion of the investigator. Any clinically significant findings from the first two subjects in the opinion of the investigator will be discussed with the Sponsor prior to dosing of the remaining 4 subjects. The dosing interval between dosing subjects in the remainder of the cohort will be at the discretion of the investigator (in consultation with the sponsor, if required) i.e. this could be increased or decreased as appropriate.

The planned starting dose of ZP-059 to be administered in MAD cohort 1 will be confirmed during an interim review of safety data from completed SAD cohorts and will not exceed a previously administered single dose. Dose administration for MAD cohort 1 will only commence after completion of review of safety data up to a minimum of 24 hours post-dose for the second dose level of Part 1 (SAD cohort 2).

There will be an interim data review before each dose escalation to the next dose level to determine safety and tolerability. The time between cohorts will be sufficient to allow this review. There will be an interim data review after completion of MAD cohort 1 and SAD cohort 3 to confirm the dose level to be administered in MAD cohort 2 and after completion of MAD cohort 2 and SAD cohort 4 to confirm the dose level to be administered in MAD cohort 3.

The data reviews described above will be conducted by the SAC, which will always comprise the Principal Investigator (or delegate) and the sponsor's medical monitor as a minimum. Full details of interim data reviews, including dose escalation criteria, are provided in Sections 6.6.1 to 6.6.4.

In the event of QD dosing subjects will receive QD doses of ZP-059 (at Hour 0) on Days 1 to 10. In the event of BID dosing, ZP-059 will be administered at Hours 0 and 12 on Days 1 to 9 and once in the morning of Day 10 (i.e. 19 doses in total). If any of the additional cohorts (i.e. Cohorts 4 and 5) are required, subjects will receive either QD or BID doses, as may be appropriate.

Details of ZP-059 are provided in the Investigational Medicinal Product Section of the

protocol.

Subjects will undergo safety, tolerability and PK (serum and sputum) evaluations at specified time points during the study (a full serum PK profile will be collected on Days 1 and 10). They will remain resident in the clinic until the morning of Day 4 after completion of dosing and safety assessments and providing there are no safety concerns.

The subjects will then return to the clinical unit daily from Day 5 through to Day 9 for pre-dose study procedures and to receive their scheduled dose (Hour 0) of study medication. On Day 7 the visit will also include induced sputum sampling pre-dose and post-dose. The subject will be discharged after dosing or sputum sampling as applicable, providing there are no safety concerns. In the event of BID dosing; on Days 4 to 9 the subjects will be required to attend the unit for the evening dose (i.e. return in the evening on Day 4 and attend twice daily on Days 5 to 9) and will be discharged after dosing providing there are no safety concerns. The subjects will then return to the clinical unit on the morning of Day 10 where they will then remain resident overnight until Day 11 (24 hours after the last dose). After completion of safety assessments, they will be discharged providing there are no safety concerns. They will return to the clinic on Days 14 and 17 for collection of PK blood samples (Day 14 only) and safety evaluations. A safety follow-up telephone call will be performed 11 to 17 days after the last dose (Day 24, +/- 3 Days) to check the status of unresolved AEs and to record any new AEs that have occurred after the last visit as well as any changes to concomitant medications.

4.1.3. Part 3 (Two-period crossover)

Part 3 is a 2-period, randomised, crossover study to assess the safety, tolerability and PK of single doses of ZP-059 compared to single doses of oral voriconazole in 16 male and female subjects with a physician confirmed documented diagnosis of mild to moderate stable asthma.

An evaluable subject for Part 3 of the study is defined as a subject who has been dosed in each treatment period and has sufficient data for evaluation of the objectives of the study.

The dose of ZP-059 will be confirmed after completion of SAD cohorts 1 to 4 and review of the available safety data. Hence, dosing of Part 3 may occur prior to/ in parallel with dosing in Part 2. The data review will be conducted by the SAC, which will comprise as a minimum the Principal Investigator (or delegate) and the sponsor's medical monitor (see Sections 6.6.1 to 6.6.4).

Eligible subjects will be randomised to receive a single dose of ZP-059 or a single oral dose of voriconazole in Period 1. Each subject then will receive the alternative treatment in Period 2 such that on completion of the study, all subjects will have received a single

dose of ZP-059 and a single oral dose of 200 mg voriconazole. The actual dose of ZP-059 will be determined at the safety review performed after completion of cohorts 1 to 4 (SAD) and will not exceed the highest dose used in Part 1.

Dosing intervals between subjects in Part 3 are not deemed necessary, however may be implemented at the discretion of the investigator (in consultation with the sponsor, if required). Subjects should be dosed at approximately the same time of day in each study period.
Subjects will be required to fast (water permitted) for at least 1 hour prior to each dose and 1 hour post each dose. The washout period between doses in each treatment period will be a minimum of 96 hours.

Subjects will undergo safety, tolerability and PK evaluations at specified time points during the study. They will remain resident in the clinic until Day 6. They will be discharged from the unit after completion of Treatment Period 2 assessments up to 24 hours post dose and providing there are no safety concerns . Subjects will return to the clinic on Days 7 and 9 for collection of 48 hour and 96 hour post dose (Treatment Period 2) PK blood and induced sputum samples (Day 7 only), and for safety evaluations to be completed. A safety follow-up telephone call will be performed 8 to 12 days after last dose to check the status of unresolved AEs and to record any new AEs that have occurred after the last visit as well as any changes to concomitant medications.

Sputum producer stratum (minimum of 6 subjects):
It is planned that a minimum of 6 out of the 16 subjects to be randomised in Part 3 will provide sufficient sputum samples at screening as per inclusion criteria 13. All subjects in Part 3 will however attempt to provide a sputum sample at the indicated timepoints as detailed in the study schedule of activities (SOA) in Section 1.2.3 (Part 3), regardless of whether they produce an adequate sample at screening.

4.2. Scientific Rationale for Study Design

This is a Phase 1, first in human (FIH) study which is aimed to test an inhaled formulation of voriconazole in healthy individuals and mild to moderate asthmatic subjects. Using an interleaved study design would allow us to switch between different interventions and give an opportunity to receive assessment data about the PK/PD profile for this new compound, safety and tolerability in both populations which would aim to develop a new approach or mode of treatment for ABPA in asthmatics in the future.

4.3. Justification for Dose

Oral Voriconazole (VFEND®): is licensed as one of the antifungals for the treatment of invasive aspergillosis at a dose of 200mg, twice daily for 3 months. Therefore, a single oral dose of 200mg in Part 3 of the study is considered safe and enough to achieve the anticipated endpoints.

ZP-059: Toxicology studies were performed to assess the maximum tolerated dose when administered to 2 beagle dogs for 12 days at increasing doses every three days at 5,10, 20 and 30mg/kg/day. Escalated doses of ZP-059, up to 21.3mg/kg/day were well tolerated. Additionally, 2 beagle dogs were administered the inhaled formulation for 14 days at a dose of 20mg/kg/day. A constant dose of 21mg/kg/day was well tolerated by both dogs throughout the 14 days. A single incidence of vomiting and reduction in food consumption during dosing was observed with 35.7mg/kg/day (Investigator's Brochure section 5.3.1).

Based on the NOAELs of the 4-week repeat-dose toxicology studies, a dose of 5mg ZP-059 was selected, which provides a conservative approach (at least 10 times lower) with adequate safety margins for the proposed human dose.

The safety margins were calculated considering the deposited dose in humans equal to the 100% of the delivered dose, further decreasing the risk and indicating that the adopted strategy can be considered satisfactory.

4.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed treatment to the end of their assigned cohort and their final safety follow up telephone call has been performed or early discontinuation visit (if applicable) i.e. last contact with the site.

The end of the study is defined as the date of the last visit or telephone contact with the last subject in the study.

5. Study Population

This protocol contains healthy subjects (Part 1), subjects with mild stable asthma (Part 2) and subjects with mild to moderate stable asthma (Part 3).

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions is not permitted.

5.1. Part 1 Eligibility Criteria

5.1.1. Part 1 Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

1. Subject's written informed consent obtained prior to any study-related procedure.
2. Healthy male and female subjects (aged ≥ 18 and ≤ 60 years at the time of informed consent.
3. Female subjects must be either of non-childbearing potential or if of childbearing potential use a highly effective birth control method (see Section 10.4.1).
4. Male subjects with female partners of childbearing potential must be vasectomised with documented medical assessment of the surgical success or use highly effective contraception together with their female partner(s) (see Section 10.4.1).
5. Subject must agree not to donate semen or ova/oocytes during the study and for 14 days after the last dose of IMP.
6. Body mass index (BMI) ≥ 18.0 and ≤ 35.0 kg/m^2 at Screening.
7. Are willing and able to comply with all aspects of the protocol.
8. FEV_1 ≥80% of the predicted value (calculated according to the Global Lung Function Initiative [GLI-2012 Quanjer [25]) and FEV_1/FVC ratio > 0.70; at screening.
9. Able to demonstrate the correct inhalation technique for use of delivery device during the study at screening and pre-dose Day 1.

5.1.2. Part 1 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Subjects who are Chinese or Japanese.
2. Subjects who have received any IMP in a clinical research study within the previous 3 months prior to Day 1.
3. Participation in other interventional studies for the duration of the study.
4. Subjects who are study site employees or immediate family members of a study site or sponsor employee.
5. History of any drug or alcohol abuse in the past 2 years prior to screening.

6. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, a 25 mL shot of 40% spirit or a 125 mL glass of wine depending on type).
7. Current tobacco or marijuana smokers and those who have smoked within the last 12 months prior to screening or prior to Day 1.
8. A confirmed positive urine cotinine test at screening or Day -1.
9. Current users of e-cigarettes or nicotine replacement products and those who have used these products within the last 12 months prior to screening or prior to Day 1.
10. Smoking history of >5 pack years at screening.
11. Females of childbearing potential who are pregnant or lactating, or who plan to become pregnant during the study. A woman is considered of childbearing potential unless she is permanently sterile (hysterectomy, bilateral salpingectomy, bilateral oophorectomy, bilateral tubal occlusion/ligation) or is postmenopausal (had no menses for 12 months without an alternative medical cause).
12. Female subject with a positive pregnancy test at screening or pre-dose on Day 1.
13. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator at screening.
14. Evidence or history of clinically significant abnormal biochemistry, haematology or urinalysis at screening, as judged by the investigator; the investigator should contact the medical monitor and /or the sponsor if required.
15. Positive urine drugs of abuse test or alcohol breath test result at screening or Day -1.
16. History of or currently infected with/carrier of human immunodeficiency virus (HIV).
17. Positive hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus (HIV) results. Subjects who are HBs antibody positive or HB core antibody positive are not excluded provided the HBsAg result is negative. Subjects who are HCV Ab positive are not excluded if a subsequent HCV RNA test is negative.
18. Evidence or history of clinically significant cardiovascular, renal, hepatic, endocrine, immunological or autoimmune, dermatological, ophthalmological, chronic respiratory or gastrointestinal disease, neurological or psychiatric disorder, as judged by the investigator.
19. Subjects with congestive heart failure or a history of congestive heart failure.
20. 12-lead ECGs demonstrating a mean QTcF interval >450 msec for males or QTcF interval >470 msec for females at screening or pre-dose Day 1.
21. History of severe cough or bronchospasm upon inhalation of any inhalation product.
22. Serious adverse reaction or serious hypersensitivity to any drug or the formulation excipients.
23. Have had allergies to or hypersensitivity reactions after administration of voriconazole or other antifungal azoles.

24. Presence or history of clinically significant allergy, including drug allergies, but excluding untreated, mild seasonal allergies, as judged by the investigator. Hay fever is allowed unless it is active.
25. Major trauma or surgery within the last 3 months prior to screening or prior to Day 1.
26. Planned or elective surgery or hospitalisations for the duration of the study that may interfere with study logistics or safety.
27. Donation or loss of more than 400 mL of blood within the previous 3 months prior to screening.
28. Subjects who are taking, or have taken, any prescribed or over-the-counter drug (other than ≤4 g per day of paracetamol, hormonal contraception or hormone replacement therapy), dietary supplements or CYP3A4 or CYP2C19 inhibitors in the 14 days (or 5 half-lives, whichever is longer) prior to Day 1 and for the duration of the study. Exceptions may apply on a case by case basis, if considered not to interfere with the objectives of the study, as agreed by the Principal Investigator and sponsor's medical monitor.
29. Subjects who are taking or have taken any herbal remedies or CYP3A4 or CYP2C19 inducers in the 28 days prior to Day 1.
30. Any use of voriconazole in the 3 months prior to Day 1.
31. Subjects who have received a live or killed/inactive vaccine in the 14 days prior to Day 1.
32. Subjects who are taking, or have taken medications that are known to prolong QTc interval in the 14 days (or 5 half-lives, whichever is longer) prior to Day 1 (Excluded medications are stated in the Study Reference Manual).
33. Upper respiratory tract infection (excluding otitis media), fever, acute or chronic cough within 14 days of Day 1, or lower respiratory tract infection within the last 4 weeks prior to Day 1.
34. Recent (within the last 4 weeks prior to Day 1) clinically significant bacterial, viral or fungal infection that required systemic (oral or intravenous) antibiotics, antivirals or antifungals; topical treatments, other than antifungals, are allowed.
35. Other social, psychiatric, surgical or medical conditions, or screening laboratory abnormalities that may increase subject risk associated with study participation or may interfere with the interpretation of study results and, in the judgement of the investigator would make the subject inappropriate for entry into the study.
36. Failure to satisfy the investigator of fitness to participate for any reason.

5.2. Part 2 Eligibility Criteria

5.2.1. Part 2 Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

1. Subject's written informed consent obtained prior to any study-related procedure.
2. Male and female subjects aged ≥ 18 and ≤ 60 years at the time of informed consent.
3. Subjects with mild stable asthma with a documented physician confirmed diagnosis of asthma for at least 3 months prior to screening.
4. Asthma assessed by investigator as being stable for at least 4 weeks prior to screening and prior to Day 1.
5. Female subjects must be either of non-childbearing potential or if of childbearing potential use a highly effective birth control method (see Section 10.4.1).
6. Male subjects with female partners of childbearing potential must be vasectomised with documented medical assessment of the surgical success or use highly effective contraception together with their female partner(s) (see Section 10.4.1).
7. Subject must agree not to donate semen or ova/oocytes during the study and for 14 days after the last dose of IMP.
8. Body mass index (BMI) ≥ 18.0 and ≤ 35.0 kg/m^2 at Screening.
9. Are willing and able to comply with all aspects of the protocol.
10. Subject is being treated with short acting beta-agonists alone or in conjunction with low to medium doses of inhaled corticosteroids (ICS). (The ICS doses allowed are stated in the Study Reference Manual).
11. Pre-bronchodilator FEV_1 ≥70% of the predicted value (calculated according to the Global Lung Function Initiative [GLI-2012 Quanjer [25]); at screening.
12. Able to understand at screening and demonstrate at pre-dose Day 1 the correct inhalation technique for use of delivery device during the study.

5.2.2. Part 2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Subjects who are Chinese or Japanese.
2. Subjects who have received any IMP in a clinical research study within the previous 3 months prior to Day 1.

3. Participation in other interventional studies for the duration of the study.
4. Subjects who are study site employees, or immediate family members of a study site or sponsor employee.
5. Subjects who have previously received IMP in this study.
6. History of any drug or alcohol abuse in the past 2 years prior to screening.
7. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, a 25 mL shot of 40% spirit or a 125 mL glass of wine depending on type).
8. Current tobacco or marijuana smokers and those who have smoked within the last 12 months prior to screening or prior to Day 1.
9. A confirmed positive urine cotinine test at screening or Day -1.
10. Current users of e-cigarettes or nicotine replacement products and those who have used these products within the last 12 months prior to screening or prior to Day 1.
11. Smoking history of >5 pack years at screening.
12. Females of childbearing potential who are pregnant or lactating, or who plan to become pregnant during the study. A woman is considered of childbearing potential unless she is permanently sterile (hysterectomy, bilateral salpingectomy, bilateral oophorectomy, bilateral tubal occlusion/ligation) or is postmenopausal (had no menses for 12 months without an alternative medical cause).
13. Female subject with a positive pregnancy test at screening or pre-dose Day 1.
14. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator at screening.
15. Evidence or history of clinically significant abnormal biochemistry, haematology or urinalysis at screening, as judged by the investigator; the investigator should contact the medical monitor and /or the sponsor if required.
16. Positive urine drugs of abuse test result (unless in the opinion of the investigator this can be explained by the subject's current medications) at screening or Day -1; unexpected positive results may require discussion with sponsor).
17. Positive alcohol breath test at screening or Day -1.
18. History of or currently infected with/carrier of HIV.
19. Positive HBsAg, HCV Ab or HIV results. Subjects who are HBs antibody positive or HB core antibody positive are not excluded provided the HBsAg result is negative. Subjects who are HCV Ab positive are not excluded if a subsequent HCV RNA test is negative.
20. Subjects who tests positive for active SARS-COV-2.

21. Evidence or history of clinically significant cardiovascular, renal, hepatic, dermatologic, ophthalmologic or gastrointestinal disease, neurological or psychiatric disorder, as judged by the investigator.
22. Evidence of history of endocrine, immunological, autoimmune disease that would affect the subject's safety or confound the assessment of study endpoints in the opinion of the investigator.
23. Current diagnosis of any chronic airways disease other than asthma such as Chronic Obstructive Pulmonary Disease, pulmonary fibrosis, CF, Churg-Strauss syndrome, bronchiectasis.
24. Evidence of ventricular dysfunction such as congestive cardiac failure (CCF) or a history of CCF assessed at screening and pre-dose Day 1.
25. 12-lead ECG demonstrating a mean QTcF interval >450 msec for males or >470 msec for females at screening or pre-dose Day 1.
26. Serious adverse reaction or serious hypersensitivity to any drug or the formulation excipients.
27. Have had allergies to or hypersensitivity reactions after administration of voriconazole or other antifungal azoles.
28. Presence or history of clinically significant allergy, including drug allergies, as judged by the investigator. Hay fever is allowed unless it is active.
29. Major trauma or surgery within the last 3 months prior to screening or prior to Day 1.
30. Planned or elective surgery, hospitalisations for the duration of the study that may interfere with study logistics or safety.
31. Donation or loss of more than 400 mL of blood within the previous 3 months prior to screening.
32. Subjects who are taking, or have taken, any prescribed or over-the-counter drugs that are CYP3A4 or CYP2C19 inhibitors in the 14 days (or 5 half-lives, whichever is longer) prior to Day 1 and for the duration of the study.
33. Subjects who are taking or have taken any herbal remedies or CYP3A4 or CYP2C19 inducers in the 28 days prior to Day 1.
34. Subjects who have received a live or killed/inactive vaccine in the 14 days prior to Day 1.
35. Presence of hoarseness or oropharyngeal candidiasis at screening or prior to dosing on Day 1.
36. Any use of voriconazole in the 3 months prior to Day 1.

37. Subjects who are taking, or have taken medications that are known to prolong QTc interval in the 14 days (or 5 half-lives, whichever is longer) prior to Day 1 (Excluded medications are stated in the Study Reference Manual).
38. History of life-threatening asthma, defined as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest and/or hypoxic seizures.
39. Hospitalisation (including accident and emergency visits) for the treatment of asthma within 3 months prior to screening or prior to Day 1 or have been hospitalised or have attended the accident and emergency for asthma more than twice in the 12 months prior to screening.
40. Occurrence of asthma exacerbations or respiratory tract infections within 4 weeks prior to screening or prior to Day 1.
41. Recent (within the last 4 weeks prior to Day 1) clinically significant bacterial, viral or fungal infection that required systemic (oral or intravenous) antibiotics, antivirals or antifungals; topical treatments, other than antifungals, are allowed.
42. Other social, psychiatric, surgical or medical conditions, or screening laboratory abnormalities that may increase subject risk associated with study participation or may interfere with the interpretation of study results and, in the judgement of the Investigator would make the subject inappropriate for entry into the study.
43. Failure to satisfy the investigator of fitness to participate for any reason.

5.3. Part 3 Eligibility Criteria

5.3.1. Part 3 Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

1. Subject's written informed consent obtained prior to any study-related procedure.
2. Male and female subjects aged ≥ 18 and ≤ 60 years at the time of informed consent.
3. Subjects with mild to moderate stable asthma with a documented physician confirmed diagnosis of asthma for at least 3 months prior to screening.
4. Asthma assessed by investigator as being stable for at least 4 weeks prior to screening and prior to randomisation.
5. Female subjects must be either of non-childbearing potential or if of childbearing potential use a highly effective birth control method (see Section 10.4.1).

6. Male subjects with female partners of childbearing potential must be vasectomised with documented medical assessment of the surgical success or use highly effective contraception together with their female partner(s) (see Section 10.4.1).
7. Subject must agree not to donate semen or ova/oocytes during the study and for 14 days after the last dose of IMP.
8. Body mass index (BMI) ≥ 18.0 and ≤ 35.0 kg/m^2 at Screening.
9. Are willing and able to comply with all aspects of the protocol.
10. Subject is being treated with low to medium doses of inhaled corticosteroids (ICS) with or without long-acting beta-agonists. (The ICS doses allowed are stated in the Study Reference Manual).
11. Pre-bronchodilator FEV_1 ≥70% of the predicted value (calculated according to the Global Lung Function Initiative [GLI-2012 Quanjer [25]); at screening.
12. Able to understand the correct inhalation technique for use of delivery device during the study at screening.
13. Sputum producer stratum only (minimum of 6 of the 16 planned subjects): Able to produce a sputum sample with a minimum weight of 50 mg at screening.

5.3.2. Part 3 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Subjects who are Chinese or Japanese.
2. Subjects who have received any IMP in a clinical research study within the previous 3 months prior to randomisation.
3. Participation in other interventional studies for the duration of the study.
4. Subjects who are study site employees, or immediate family members of a study site or sponsor employee.
5. Subjects who have previously received IMP in this study.
6. History of any drug or alcohol abuse in the past 2 years prior to screening.
7. Regular alcohol consumption in males >21 units per week and females >14 units per week (1 unit = ½ pint beer, a 25 mL shot of 40% spirit or a 125 mL glass of wine depending on type).
8. Current tobacco or marijuana smokers and those who have smoked within the last 12 months prior to screening or prior to randomisation.
9. A confirmed positive urine cotinine test at screening or prior to randomisation.

10. Current users of e-cigarettes or nicotine replacement products and those who have used these products within the last 12 months prior to screening or prior to randomisation.
11. Smoking history of >5 pack years at screening.
12. Females of childbearing potential who are pregnant or lactating, or who plan to become pregnant during the study. A woman is considered of childbearing potential unless she is permanently sterile (hysterectomy, bilateral salpingectomy, bilateral oophorectomy, bilateral tubal occlusion/ligation) or is postmenopausal (had no menses for 12 months without an alternative medical cause).
13. Female subject with a positive pregnancy test at screening or prior to randomisation.
14. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the investigator at screening.
15. Evidence or history of clinically significant abnormal biochemistry, haematology or urinalysis at screening, as judged by the investigator; the investigator should contact the medical monitor and /or the sponsor if required.
16. Positive urine drugs of abuse test result (unless in the opinion of the investigator this can be explained by the subject's current medications) at screening or prior to randomisation; unexpected positive results may require discussion with sponsor).
17. Positive alcohol breath test at screening or prior to randomisation.
18. History of or currently infected with/carrier of HIV.
19. Positive HBsAg, HCV Ab or HIV results. Subjects who are HBs antibody positive or HB core antibody positive are not excluded provided the HBsAg result is negative. Subjects who are HCV Ab positive are not excluded if a subsequent HCV RNA test is negative.
20. Subjects who tests positive for active SARS-COV-2.
21. Evidence or history of clinically significant cardiovascular, renal, hepatic, dermatologic, ophthalmologic or gastrointestinal disease, neurological or psychiatric disorder, as judged by the investigator.
22. Evidence of history of endocrine, immunological, autoimmune disease that would affect the subject's safety or confound the assessment of study endpoints in the opinion of the investigator.
23. Current diagnosis of any chronic airways disease other than asthma such as Chronic Obstructive Pulmonary Disease, pulmonary fibrosis, CF, Churg-Strauss syndrome, bronchiectasis.
24. Evidence of ventricular dysfunction such as congestive cardiac failure (CCF) or a history of CCF assessed at screening and prior to randomisation.

25. 12-lead ECG demonstrating a mean QTcF interval >450 msec for males or >470 msec for females at screening or prior to randomisation.
26. Serious adverse reaction or serious hypersensitivity to any drug or the formulation excipients.
27. Have had allergies to or hypersensitivity reactions after administration of voriconazole or other antifungal azoles.
28. Presence or history of clinically significant allergy, including drug allergies, as judged by the investigator. Hay fever is allowed unless it is active.
29. Major trauma or surgery within the last 3 months prior to screening or prior to randomisation.
30. Planned or elective surgery, hospitalisations for the duration of the study that may interfere with study logistics or safety.
31. Donation or loss of more than 400 mL of blood within the previous 3 months prior to screening.
32. Subjects who are taking, or have taken, any prescribed or over-the-counter drugs that are CYP3A4 or CYP2C19 inhibitors in the 14 days (or 5 half-lives, whichever is longer) prior to randomisation and for the duration of the study.
33. Subjects who are taking or have taken any herbal remedies or CYP3A4 or CYP2C19 inducers in the 28 days prior to randomisation.
34. Subjects who have received a live or killed/inactive vaccine in the 14 days prior to randomisation.
35. Presence of hoarseness or oropharyngeal candidiasis at screening or prior to randomisation.
36. Any use of voriconazole in the 3 months prior to randomisation.
37. Subjects who are taking, or have taken medications that are known to prolong QTc interval in the 14 days (or 5 half-lives, whichever is longer) prior to randomisation (Excluded medications are stated in the Study Reference Manual).
38. History of life-threatening asthma, defined as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest and/or hypoxic seizures.
39. Hospitalisation (including accident and emergency visits) for the treatment of asthma within 3 months prior to screening or prior to randomisation or have been hospitalised or have attended the accident and emergency for asthma more than twice in the 12 months prior to screening.
40. Occurrence of asthma exacerbations or respiratory tract infections within 4 weeks prior to screening or prior to randomisation.

41. Recent (within the last 4 weeks prior to randomisation) clinically significant bacterial, viral or fungal infection that required systemic (oral or intravenous) antibiotics, antivirals or antifungals; topical treatments, other than antifungals, are allowed.
42. Other social, psychiatric, surgical or medical conditions, or screening laboratory abnormalities that may increase subject risk associated with study participation or may interfere with the interpretation of study results and, in the judgement of the Investigator would make the subject inappropriate for entry into the study.
43. Failure to satisfy the investigator of fitness to participate for any reason.

5.4. Lifestyle Considerations

5.4.1. Meals and Dietary Restrictions

1. Subjects must not drink liquids or eat food containing grapefruit, starfruit or cranberry or consume red wine, from 24 hours prior to admission on Day -1 until discharge (24 hours post-dose for Parts 1 and 3 (post Treatment Period 2 dose), and the morning of Day 11 for Part 2; i.e. through to 24 hours post last dose in a treatment period).
2. Subjects must fast (water permitted) for at least 8 hours prior to clinical chemistry safety blood samples.
3. Subjects must fast (water permitted) for at least 1 hour prior to dosing and 1 hour post-dose. In the event of BID dosing in Part 2 this restriction will apply to both the 0 hour and the 12 hour doses.
4. When subjects are confined in the clinical unit, meals and snacks will be provided at appropriate times, except when subjects are required to fast. When confined in the clinical unit, subjects will be required to fast from all food and drink except water between meals and snacks.

5.4.2. Caffeine and Alcohol

1. Subjects must abstain from alcohol for 24 hours prior to and during all visits.
2. Subjects must not drink liquids or eat food containing caffeine or other xanthines from 24 hours prior to and during all visits. Decaffeinated beverages are allowed.

5.4.3. Activity

1. Subjects must not take part in any unaccustomed strenuous exercise from the 72 hours prior to and during all visits.

5.4.4. Additional Study Restrictions

1. It is recommended that all subjects avoid exposure to direct sunlight and use measures such as protective clothing and sunscreen with high sun protection factor (SPF) from admission on Day -1 until 72 hours post last dose.

5.5. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but who do not subsequently receive IMP. A minimal set of data from all subjects who are screen failures will be required to be entered into the CRF.

5.6. Subject Re-Screening

Re-screening will be allowed for a subject who has discontinued the study as eligible-but-not-required (i.e. reserves) or could not be dosed within the permitted screening window for any reason, or as a pre-treatment failure (i.e., subject has not been treated); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re-consented.

Re-screened subjects should be assigned a new screening number at the time of re-consent.

6. Investigational Medicinal Products

ZP-059 inhaled voriconazole is manufactured according to Good Manufacturing Practices (GMPs) by MICRO-SPHERE S.A. CH – 6998 Monteggio, packaged and QP released by STM PHARMA PRO srl Italy.

ZP-059 inhaled voriconazole contains Voriconazole as active pharmaceutical ingredient.

The chemical name for Voriconazole is: (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol.

ZP-059 inhaled voriconazole is provided in clear, colourless size 3 hydroxypropylmethylcellulose (HPMC) hard capsules. The hard capsules are individually and manually triggered by breath actuated inhalation device. The capsules are packaged in aluminium-aluminium blisters.

The formulation strength is expressed as delivered dose; the strength, expressed as metered dose on unit basis, is voriconazole 5.74 mg inhalation powder.

The composition of the formulation ZP-059 inhaled voriconazole and the amount of ingredients on a unit basis, the function of the components as well as the reference to their quality standard is presented in Table

Table 2 Composition of ZP-059 (inhaled voriconazole capsule)

Components	Amount mg/capsule	% w/w	Function	Quality Standard*
Voriconazole *Corresponding to mg/inhalation*	5.74 5.0	70.00	Active Substance	Ph. Eur.
L-Leucine	2.378	29.00	Disaggregation agent	Ph. Eur.
Polysorbate 80	0.082	1.00	Dissolution agent	Ph. Eur.
Purified Water [1]	q.s.	-	Solvent-process agent	Ph. Eur.
Ethanol, anhydrous [2]	q.s.	-	Solvent-process agent	Ph. Eur.
HPMC [3] hard capsules size 3	(1)		Powder container	In-house
Total powder weight *per* capsule	8.20	100.00		

[1] Removed during processing
[2] Removed during processing
[3] HPMC = hydroxypropyl methylcellulose
q.s.= *quantum satis*

* current Edition of Ph. Eur. is endorsed

Polysorbate 80 is a common excipient for inhalation products as its use is widely accepted inside liquid and pressurised formulations and it has been incorporated into the formulation to allow for rapid dissolution and dispersion of the active component.

L-leucine is a naturally occurring amino-acid whose purpose in the formulation is to facilitate the deagglomeration of the particles during the inhalation.

In Part 3, VFEND® oral film-coated 200 mg tablet, a currently marketed oral voriconazole formulation, will be administered. The dose of VFEND® will be a single dose of 200 mg, which is the recommended dose of the marketed product.

Provision of the ZP-059 5 mg capsules (nominal voriconazole dose strength 5 mg) and DPIs will be the responsibility of Zambon. VFEND® 200mg tablets, will be sourced from the UK and labelled for clinical use by MEU.

Test IMP: Dry powder for oral inhalation with a formulation comprising voriconazole as the active ingredient; Edry-Voriconazole 5 mg capsule **ZP-059**

Reference IMP (Part 3): VFEND® oral film-coated tablet (200 mg); a currently marketed oral voriconazole formulation by Pfizer Limited, UK.

Dry Powder Inhaler for administration of voriconazole capsules: RS01 inhaler (RS01 Monodose inhaler, product code 239700004AA)

The DPI used for inhalation of voriconazole capsules is the RS01 inhaler (RS01 Monodose inhaler, Model 7 high-resistance, product code 239700004AA), manufactured by Plastiape, S.p.A. This device is CE-marked for use in the European Union. The RS01 is a passive DPI, utilising the subject's inhalation flow to disperse and deliver the drug formulation. The DPI is a reloadable, single capsule device that uses pre-metered, size 3 HPMC capsules. The DPI will be manufactured and supplied according to Good Manufacturing Practices (GMP) for use in the clinical trial.

Details of the IMPs to be used in each study part are provided in Table 3.

All IMPs will be reconciled and destroyed upon approval by the sponsor in accordance with site's SOPs.

6.1. Administration of Investigational Products

Specific details of IMPs and doses to be administered are provided in Table 2 below. For all study parts, subjects will be dosed on each study period/dosing day, as applicable.

The exact time of dosing will be decided based on logistics and will be documented in the source records.

Subjects in Part 1 will receive a total of 1 administration of ZP-059 on one occasion. Subjects in Part 2 will receive a total of 10 administrations of ZP-059 on 10 separate occasions (based on the dosing frequency of q.d.) or in the event of BID dosing they will receive a total of 19 doses. Subjects in Part 3 will receive a total of 1 administration of ZP-059 on one occasion and a total of 1 administration of oral voriconazole (VFEND®) on one occasion.

Detailed instructions for dose administration will be provided in a pharmacy manual. The start and end time of dosing (i.e. first and last capsule dose times) will be recorded in the source data. For the purposes of PK sampling and post-dose procedures, the time of inhalation of the first capsule will be the dose time and thus time ‘0’.

For Part 3, the subjects will be required to swallow the VFEND® tablet whole with some water.

Table 3 Investigational Medicinal Products

Study Part	Cohort	IMP	Dose and Route of Administration
1	SAD 1	ZP-059	5 mg (1 x 5 mg capsule) ZP-059 [a] Administered via DPI on Day 1
	SAD 2	ZP-059	ZP-059 (Dose TBD) Administered via DPI on Day 1
	SAD 3	ZP-059	ZP-059 (Dose TBD) Administered via DPI on Day 1
	SAD 4	ZP-059	ZP-059 (Dose TBD) Administered via DPI on Day 1
2	MAD 1	ZP-059	ZP-059 (Dose TBD) Administered via DPI once daily on Days 1 to 10 or twice daily on Days 1 to 9 and once on Day 10
	MAD 2	ZP-059	ZP-059 (Dose TBD) Administered via DPI once daily on Days 1 to 10 or twice daily on Days 1 to 9 and once on Day 10
	MAD 3	ZP-059	ZP-059 (Dose TBD) Administered via DPI once daily on Days 1 to 10 or twice daily on Days 1 to 9 and once on Day 10
Study Part	Treatment Period	IMP	Dose and Route of Administration
3	1 or 2	ZP-059	ZP-059 (Dose TBD) Administered via DPI on Day 1 of Period 1 or Period 2
		Voriconazole (VFEND®) oral film-coated tablet	200 mg Voriconazole (VFEND® - oral film-coated tablet) on Day 1 of Period 1 or Period 2

[a] Fixed starting dose
DPI; dry powder inhaler
TBD; to be determined
Each capsule delivers 5 mg of voriconazole

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMPs received and any discrepancies are reported and resolved before use of the IMP.
2. Only subjects who meet eligibility criteria for the study may receive study IMP and only authorised site staff may supply or administer IMP. All IMP must be stored in

a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorised site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of used and unused study IMP are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomisation and Blinding

6.3.1. Randomisation

Parts 1 and 2 are an open-label, non-randomised design, therefore a randomisation schedule will not be produced.

Part 3 is a randomised, open-label design; therefore, a randomisation schedule will be produced.

The original randomisation schedule for Part 3 and proof of quality control procedures will be held by SQN Clinical until the study is archived, at which time the randomisation materials will be retained in the Investigator Site File (ISF). Subjects will be randomised immediately before administration of the first dose.

6.3.2. Subject Numbers

In Part 1, subject numbers will be allocated on the morning of dosing according to the code 101 to 130 using the lowest number available. In case of subject replacement, the subject will be assigned a number from 101R to 130R with the same first three digits as the original subjects. In case of a second replacement, the replacement subject will be assigned a number from 101S to 130S. In case of third replacement, the replacement subject will be assigned a number from 101T to 130T.

In Part 2, subject numbers will be allocated on the morning of dosing on Day 1 according to the code 201 to 230 using the lowest number available. In case of subject replacement, the subject will be assigned a number from 201R to 230R with the same first three digits as the original subjects. In case of a second replacement, the replacement subject will be assigned a number from 201S to 230S. In case of third replacement, the replacement subject will be assigned a number from 201T to 230T.

In Part 3, subject numbers will be allocated on the morning of dosing during Period 1 according to the code 301 to 316 using the lowest number available. In case of subject replacement, the subject will be assigned a number from 301R to 316R with the same first three digits as the original subjects. In case of a second replacement, the

replacement subject will be assigned a number from 301S to 316S. In case of third replacement, the replacement subject will be assigned a number from 301T to 316T.

6.3.3. Blinding

This is an open-label study and therefore blinding is not required.

6.4. Investigational Product Compliance

During all clinical phases of the study, subjects will be observed by study staff to assure compliance to all study procedures, including dose administration.

For Part 3, mouth and dosing vessel checks will be conducted after dose administration of oral voriconazole to ensure the tablet has been swallowed.

For all study parts, the date and time that each subject is dosed will be recorded in the subject's source record. Any violation of compliance will require evaluation by the investigator and sponsor to determine if the subject can continue in the study.

6.5. Concomitant Therapy

6.5.1. Prior and Concomitant Medications

Any medications used will be recorded in the source records. Any prior medications taken within 28 days prior to screening and all concomitant medications will be recorded in the eCRF.

6.5.2. Permitted Concomitant Medications for Part 1 (SAD)

No medication will be permitted from 14 days before IMP administration until the follow-up visit except hormonal contraceptives, hormone replacement therapy (HRT), ≤4 g per day paracetamol and those deemed necessary by the investigator to treat AEs.

Exceptions may apply on a case by case basis, if considered not to interfere with the objectives of the study (and are not a prohibited medication), as agreed by the Principal Investigator and sponsor's medical monitor.

Emergency equipment and drugs will be available within the clinical unit as per current standard procedures. In the event that they are required, their use will be documented.

6.5.3. Permitted Concomitant Medications for Part 2 (MAD) and Part 3 Crossover)

During Part 2 and Part 3 of the study subjects will be permitted to take the following medications in addition to IMP during the study.

6.5.3.1. Part 2 and Part 3

- Inhaled corticosteroids (ICS) e.g. beclometasone, budesonide, only if the dose is stable from at least 4 weeks prior to screening. On study dosing days, the morning dose should be taken prior to pre-dose spirometry. Evening doses should be taken as logistics allow.
- Short-acting beta-agonists (SABA; e.g. salbutamol, terbutaline). At screening, SABA should be withheld for at least 6 hours prior to pre-bronchodilator spirometry. On study dosing days, SABA should be used as required per subject's symptoms and as required by site-specific SOPs for sputum induction.
- Paracetamol (≤4 g per day).
- Hormonal contraception.
- Hormone replacement therapy (HRT).
- Any medication taken at a stable dose for at least 4 weeks prior to IMP administration that is not specifically prohibited by Section 6.5.4. and is not believed to interfere with the study assessments is acceptable e.g. stable thyroxine, antihypertensives, metformin etc.
- Medication deemed necessary by the investigator to treat AEs.

6.5.3.2. Part 3

- Long-acting beta-agonists (LABA) e.g. formoterol, salmeterol. At screening, LABA should be with-held for at least 12 hours prior to pre-bronchodilator spirometry. On study dosing days, the morning dose should be taken prior to pre-dose spirometry. Evening doses should be taken as logistics allow.
- Ultra-long acting beta-agonist e.g. indacaterol. At screening, ultra-long LABA should be with-held for at least 24 hours prior to pre-bronchodilator spirometry. On study dosing days, the morning dose should be taken prior to pre-dose spirometry. Evening doses should be taken as logistics allow.
- ICS/LABA combination products (e.g. fluticasone + salmeterol, budesonide + formoterol), only if the dose has been stable from at least 4 weeks prior to screening. At screening ICS/LABA should be withheld for at least 12 hours prior to pre-bronchodilator spirometry. On study dosing days, the morning dose should be taken prior to pre-dose spirometry. Evening doses should be taken as logistics allow.

- ICS/ultra-long acting beta-agonist e.g. fluticasone + vilanterol. At screening ICS/ultra-long acting beta- agonist should be withheld for 24 hours prior to pre-bronchodilator spirometry. On study dosing days, the morning dose should be taken prior to pre-dose spirometry. Evening doses should be taken as logistics allow.

If a required inhaled medication with-hold has not been met at the screening visit, the visit and/or spirometry assessment may be rescheduled at the discretion of the investigator.

Emergency equipment and drugs will be available within the clinical unit as per current standard procedures. In the event that they are required, their use will be documented.

6.5.4. Prohibited Concomitant Medications

Parts 1, 2 and 3

- Voriconazole is prohibited for 3 months prior to first IMP administration and throughout the study.
- Specific enzyme inducers of CYP3A4 and CYP2C19 are prohibited for 28 days prior to first IMP administration until 14 days after last IMP administration.
- Specific enzyme inhibitors, substrates of CYP3A4 and CYP2C19 are prohibited for 14 days (or 5 half-lives, whichever is longer) prior to first IMP administration until 14 days (or 5 half-lives, whichever is longer) after last IMP administration.
- Any systemic treatment for infection is prohibited in the 28 days prior to first IMP administration e.g. amoxicillin, aciclovir.
- Live and killed/inactive vaccines are prohibited in the 14 days prior to first IMP administration and throughout the study.
- Medications that are known to prolong QTc interval in the 14 days (or 5 half-lives, whichever is longer) prior to first IMP administration and throughout the study (Excluded medications are stated in the Study Reference Manual).
- Long-acting muscarinic antagonists (LAMA) e.g. tiotropium for at least 28 days prior to first IMP administration.
- Short-acting muscarinic antagonists (SAMA); e.g. ipratropium for at least 12 hours prior to screening pre-bronchodilator spirometry and throughout the study.
- Oral corticosteroids for at least 28 days prior to first IMP administration.
- Omalizumab for at least 28 days prior to first IMP administration.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6. Criteria for Dose Escalation

Dose escalation decisions will be made by the SAC, which will always comprise as a minimum the Principal Investigator (or delegate) and the sponsor's medical monitor. Additional data available at the time of each scheduled meeting may also be reviewed. For all dose escalation decisions, the critical data will be safety data. The criteria to be followed by the SAC are detailed in Section 6.6.4.

Data will be provided to the SAC in accordance with the site's SOP on dose escalation/continuation in clinical trials. The decisions will be documented and signed by the Principal Investigator (or delegate) per the current SOP. Evidence of the decision will be retained in the ISF and Trial Master File maintained by MEU.

Dose escalation/dose decision procedures for each study part are described below.

6.6.1. Part 1 (SAD)

Dose escalation decisions will be made at an interim data review after dose administration for each cohort. Progression to the next dose group will be permitted after review of safety data suggests that it is safe to do so.

For dose escalation to proceed, data must be available from a minimum of 4 dosed subjects who have completed the planned safety assessments up to a minimum of 24 hours after dosing. The decision to proceed will only be made if all parties agree and if it is clear from the safety data that it is appropriate to proceed with the next cohort. If data in fewer than 6 subjects are considered acceptable to proceed, additional subjects will not be dosed to increase the number of subjects in the completed cohort for dose escalation purposes.

Based on the observed data, it may be necessary or desirable to administer a previously administered dose, a reduced dose or a dose level higher than planned in order to determine the safe starting dose for Part 2 of the study. An additional cohort of 6 subjects may be enrolled to assess this. Single doses will not exceed 40 mg of ZP-059 based on safety margins calculated following non-clinical studies.

6.6.2. Part 2 (MAD)

Dose administration in Part 2 may only commence after completion of SAD cohort 2 in Part 1 and review of safety data up to a minimum of 24 hours post-dose.

The decision to proceed with Part 2 and dose escalation decisions between MAD cohorts will be made at an interim data review after dose administration in each cohort.

Progression to the next dose group will be permitted after review of safety data suggests that it is safe to do so.

The starting dose for Part 2 MAD will be confirmed during an interim review of safety data from the completed SAD cohorts. The dose to be administered in MAD cohort 2 will be based on emerging data and will not exceed the highest dose investigated in the SAD cohorts.

For dose escalation to proceed in MAD cohort 2, data must be available from a minimum of 4 dosed subjects from MAD cohort 1 (defined in Section 4.1.2) who have completed the planned safety assessments up to a minimum of 24 hours after dosing on Day 10 and up to a minimum of 24 hours post-dose from SAD cohort 3. For dose escalation to proceed in MAD cohort 3, data must be available from a minimum of 4 dosed subjects from MAD cohort 2 (defined in Section 4.1.2) who have completed the planned safety assessments up to a minimum of 24 hours after dosing on Day 10 and up to a minimum of 24 hours post-dose from SAD cohort 4.

The decision to proceed will only be made if all parties agree and if it is clear from the safety data that it is appropriate to proceed with the next cohort. If data in fewer than 6 subjects are considered acceptable to proceed, additional subjects will not be dosed to increase the number of subjects in the completed cohort for dose escalation purposes.

6.6.3. Part 1 (SAD) to Part 3

The oral dose of voriconazole to be administered in Part 3 is 200 mg.

The inhaled ZP-059 dose to be administered in Part 3 will be confirmed after completion of SAD cohorts 1 to 4. Hence, dosing of Part 3 may occur prior to/in parallel with dosing in Part 2.

The dose decision will be made at an interim review of available safety data from Part 1 SAD cohorts (see Section 6.6.1). For dose administration to proceed, data must be available from a minimum of 4 dosed subjects in each of SAD cohorts 1, 2, 3 and 4 who have completed the planned safety assessments up to a minimum of 24 hours after dosing. The decision to proceed will only be made if all parties agree and if it is clear from the safety data that it is appropriate to proceed.

6.6.4. Criteria for Safety Advisory Committee

Dose levels for each cohort (Parts 1 and 2) and Part 3 will be decided during the SAC meetings.

The SAC may also agree for additional subjects to be included for an intermediate dose level if warranted or may agree to reduce or increase (see Section 4.3) the dose. Any decision to investigate an intermediate or reduced dose level will be fully documented.

The decision to proceed to the next higher dose level will be based on safety and tolerability data. The following data (minimum of 24 hours post-dose) are required for dose escalation decisions:

- Adverse events
- Vital signs (including systolic and diastolic blood pressure, pulse rate, respiratory rate and pulse oximetry)
- Safety laboratory (including clinical chemistry, haematology and urinalysis)
- ECG
- Physical examinations
- Spirometry assessments (including FEV_1, forced vital capacity [FVC], peak expiratory flow rate [PEFR] and FEV_1/FVC)

If, following review by the SAC it is deemed acceptable to continue dose escalation above the maximum dose described in this protocol (40 mg ZP-059), a substantial amendment with relevant data will be submitted for approval to the regulatory authorities and ethics committee (EC).

Dose escalation will not occur if:

- One or more subjects in a cohort experiences a serious adverse event (SAE) related to IMP.

  or
- Two or more subjects in a cohort experiences severe non-serious AEs related to IMP.

6.6.5. Stopping Criteria

6.6.5.1. Part 1, Part 2 and Part 3

All parts of the study will be halted, if any of the following criteria are met:

- The occurrence of an SAE considered related to the IMP administration in 1 subject.
- The occurrence of severe, non-serious AEs considered related to the IMP administration in 2 subjects at the same dose level (Part 1 and Part 2).

- The occurrence of severe, non-serious AEs considered related to the IMP administration in 2 subjects receiving the same treatment (i.e. 2 subjects receiving ZP-059 or 2 subjects receiving oral voriconazole) in Part 3.

Relatedness will be determined by the investigator (see Section 10.3.3). If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and EC in the form of a substantial amendment. The study will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

7. Discontinuation of Investigational Medicinal Product and Subject Discontinuation/Withdrawal

7.1. Discontinuation of Investigational Medicinal Product

Subjects will be withdrawn from IMP for the following reasons:

- Subjects will be withdrawn from IMP if they exhibit a SAE and/or any AEs that in the opinion of the PI may jeopardise their safety.
- QTcF interval of >500 msec or increase in QTcF interval of >60 msec from baseline.
  For the purpose of QTcF withdrawal criteria, baseline will be considered as the mean pre-dose Day 1 measurement for Parts 1 and 2, and the mean pre-dose Day 1 measurement of each treatment period for Part 3 (i.e. baseline for Period 1 is pre-dose on Day 1 Period 1; baseline for Period 2 is pre-dose on Day 1 Period 2). The withdrawal criterion will be assessed against the mean QTcF of triplicate ECGs and confirmed by a repeat triplicate ECG. ECGs will be performed within a time window of 5 minutes, with minimum of 1 minute between subsequent ECGs
- Increase of total bilirubin greater than or equal to 3x the upper level of normal
- Increase of liver enzyme (AST, ALT) value greater than or equal to 3x the upper level of normal. Asymptomatic subjects with a liver enzyme [AST, ALT] greater than or equal to 2x the upper level of normal but less than or equal to 3x the upper level of normal will be retested, as required.
- Pregnancy of a female subject or female partner of a male subject
- Upon the subject's request (withdrawal of consent)
- Significant deviation from the protocol that is considered, in the opinion of the investigator or sponsor, to jeopardise the subject's safety
- Requirement for prohibited medication
- At the discretion of the investigator
- Termination of the study for any reason by the sponsor.
- Parts 1 only: Any drug-induced bronchoconstriction requiring treatment
- Part 2 and 3 only: Exacerbation of asthma requiring systemic treatment

For a subject who withdraws or is withdrawn every effort will be made to ensure the subject completes early discontinuation procedures (if applicable) as soon as possible after discontinuation and as detailed in the study schedule of activities (SOA) in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). A safety follow-up call will also be performed, if possible, if the early discontinuation visit has been performed prior to the scheduled follow up period.

7.2. Subject Replacement

Subjects who withdraw or are withdrawn from the study may be replaced at the discretion of the Sponsor.

7.3. Subject Discontinuation/Withdrawal from the Study

- A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, early discontinuation procedures (if applicable) as detailed in the study schedule of activities (SOA) in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3) should be performed as soon as possible after discontinuation. A safety follow-up call will also be performed, if possible, if the early discontinuation visit has been performed prior to the scheduled follow up period.
- The subject will be permanently discontinued both from the study medication and from the study at that time.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.4. Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known

mailing address or local equivalent methods). These contact attempts should be documented in the subject's source data records.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of the study are handled as part of Appendix 1.

8. Study Assessments and Procedures

Study procedures will be performed as detailed in the study schedule of activities (SOA) in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3), and in accordance with site SOPs unless otherwise stated in this protocol.

8.1. Screening

Within the 28 days preceding first dose, all subjects will be required to undergo a screening visit. Screening procedures will be carried out in accordance with the SoA in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3).

Screening procedures may be performed over more than 1 day. Repeats of study procedures are permitted on the day and/or on another day during screening at the discretion of the investigator(s).

For Part 2 subjects who completed the initial Screening Visit will attend the Clinic on Day -4 or Day -3, for a SARS-COV-2 RT-PCR test. This may be performed on the same day as screening if screening is performed within 3 or 4 days of dosing.

For Part 3 subjects will undergo a SARS-COV-2 RT-PCR test prior to sputum induction at screening. SARS-COV-2 RT-PCR test must be performed within 14 days of Day 1, Period 1. If this interval is exceeded, sampling must be repeated.

8.2. Admission and Pre-dose Procedures

For all study parts, the subjects will be admitted to the clinic on the evening of Day -1 and the ongoing eligibility of subjects will be re-assessed at admission/pre-dose (as applicable), as described in Sections 5.1 to 5.3.

8.3. Device Training

For Parts 1, 2 and the relevant treatment period in Part 3, subjects will undergo inhalation training in order to ensure optimal dosing. The subjects will undergo device training to achieve a steady, slow and deep inhalation. Device training will be performed using an empty RS01 inhaler. Training at screening will be for demonstration purposes only. Full details of inhalation training are given in the pharmacy manual.

The admission and pre-dose procedures for Parts 1, 2 and 3 are presented in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3) respectively.

8.4. Blood Volume

The total blood volume for each subject will not exceed 400 mL in a 4-week period.

At least the first 1 mL of blood withdrawn via cannula will be discarded; this will be based on local SOPs.

8.5. Timing of Procedures

Permitted windows for all relevant procedures and dosing will be provided in the Study Reference Manual. Where the protocol requires more than one procedure to be completed at the same time point, all efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Any other procedures scheduled at the same time point will be performed either before or after the PK, as appropriate.

ECGs should be taken prior to vital signs when both measurements are scheduled at the same time point. Other assessments e.g. spirometry, physical examinations, etc. will be performed within the required time windows. Assessments taken in a different order for logistical reasons will not be considered protocol deviations provided that the required rest times have been respected for ECGs and vital signs.

All safety assessments will be timed and performed relative to the start of dosing (defined as time of first capsule inhalation).

8.6. Discharge from the Clinical Unit

A subject will be allowed to leave the clinical unit following completion of the 24-hour post-dose study-specific procedures (Day 2 in Part 1, Day 6 in Part 3) and at 24 hours after dosing on Day 4 (Part 2) and providing there are no safety concerns.

8.7. Return Visits

Part 1:

Subjects will be required to return to the clinical unit on Day 5 for completion of safety evaluations (see Section 1.2.1).

Part 2:

Subjects will be required to return to the clinical unit daily from Day 5 through to Day 9 for pre-dose study procedures and to receive their scheduled dose (Hour 0) of study medication. On Day 7 the visit will also include induced sputum sampling pre-dose and post-dose. The subject will be discharged after dosing or sputum sampling as applicable, providing there are no safety concerns. In the event of BID dosing; on Days 4 to 9 the subjects will be required to attend the unit for the evening dose (i.e. return in the evening on Day 4 and attend twice daily on Days 5 to 9) and will be discharged after dosing, providing there are no safety concerns. The subjects will then return to the clinical unit on the morning of Day 10 where they will then remain resident overnight until Day 11 (24

hours after the last dose). After completion of safety assessments, they will be discharged providing there are no safety concerns.

Subjects will be required to return to the clinical unit on Day 14 and Day 17 for collection of PK samples (Day 14 only) and completion of safety evaluations (see Section 1.2.2 (Part 2)).

Part 3:

Subjects will be required to return to the clinical unit on Day 7 (48 hours post treatment period 2 dose) and Day 9 (96 hours post treatment period 2 dose) for collection of PK blood samples, induced sputum samples (Day 7 only), and completion of safety evaluations (see Section 1.2.3).

For all study parts; permitted windows for all relevant procedures (including dosing when appropriate) will be provided in the Study Reference Manual.

8.8. Medical Supervision

A physician will be responsible for the clinical aspects of the study and will be available at all times during the study. In accordance with the current Association of the British Pharmaceutical Industry guidelines [22], each subject will receive a card stating the telephone number of the investigator.

8.9. Follow-up

A safety follow-up telephone call will take place in accordance with the SoA in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3) to all subjects after their last dose to ensure their ongoing wellbeing. In the event of early discontinuation, the telephone call will not be required if the early discontinuation visit is performed within the scheduled follow up period.

If a subject reports any AEs that may present a cause for concern, they will be required to attend the clinic for a further follow-up assessment (as an unscheduled visit).

8.10. Efficacy Assessments

Not applicable for this Phase I study.

8.11. Safety Assessments

8.11.1. Physical Examinations

Subjects will undergo a physical examination at screening as detailed in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). A full physical examination will involve assessment of the following: general appearance; head, neck and thyroid; ears, nose and throat; cardiovascular; respiratory; lymph nodes; abdomen; skin; musculoskeletal and nervous system. A symptom directed physical examination will involve any body system deemed necessary at the investigator's discretion due to on-going AEs at the time of assessment. Any clinically significant changes will be recorded as AEs.

8.11.2. Vital Signs

Blood pressure, pulse rate and respiratory rate will be measured after the subject has been in a supine position for a minimum of 5 minutes according to the schedule of activities presented in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). Repeat tests are permitted on the day and/or on another day (as appropriate) at the discretion of the investigator. Blood pressure and pulse rate will be measured by automated equipment. Temperature will be measured according to the schedule of activities presented in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3).

8.11.3. Body, Weight and Height

The subject's body weight and height will be recorded as detailed in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). Measurements will be taken in normal indoor clothing with shoes removed.

8.11.4. Pulse Oximetry

Oxygen saturation via pulse oximetry will be measured as detailed in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3).

8.11.5. Electrocardiograms

Scheduled 12-lead ECGs will be measured in triplicate after the subject has been in the supine position for a minimum of 5 minutes according to the schedule of activities presented in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). Repeats are permitted on the day and/or on another day (as appropriate) at the discretion of the investigator. ECGs will be performed within a time window of 5 minutes, with

minimum of 1 minute between subsequent ECGs. Mean triplicate ECGs will be used for the purpose of summary statistics (see Section 7.1 for definition of baseline for each study part).

For assessment of time windows, the time of the first ECG of the triplicate will be used.

8.11.6. Pulmonary Function Tests

Pulmonary function tests will be performed to determine parameters as detailed below. The following lung function tests will be performed using a standard calibrated spirometer:

- forced expiratory volume in 1 sec (FEV_1)
- forced vital capacity (FVC)
- peak expiratory flow rate (PEFR)
- FEV_1/FVC

The tests will be performed according to the schedule of activities presented in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). Predicted values will be calculated according to GLI-2012 Quanjer [25] and adjusted for age, gender and race. Throughout the study, age at the time of each spirometry assessment will be used for assessment of predicted values.

For Part 2 and Part 3, reversibility at screening will be assessed by performing pre-bronchodilator spirometry after withholding SABA for at least 6 hours and LABA for at least 12 hours or at least 24 hours for Ultra-long acting LABA. Subsequent to pre-bronchodilator spirometry, 400 µg salbutamol will be administered via a spacer. Post-bronchodilator spirometry will be performed with first manoeuvre commencing within 15 to 30 minutes of salbutamol administration.

8.11.7. Sputum Induction (Part 2 and Part 3 only)

Sputum induction will be performed according to the schedule of activities presented in Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3) and in accordance with European Respiratory Society guidelines [23] and site-specific SOPs. The start time of the sputum induction will be recorded as the first inhalation of saline.

8.11.8. Procedures In case of Bronchospasm

For all parts of the study, salbutamol via metered dose inhaler plus spacer and nebuliser, and oxygen will be immediately available if required for the treatment of bronchospasm/ bronchoconstriction.

8.11.9. Part 1 (Healthy Subjects)

Any subject requiring treatment for bronchoconstriction will have their FEV_1 monitored frequently until their FEV_1 has returned to within 90% of their baseline value or to a level considered acceptable by the investigator.

8.11.10. Part 2 and Part 3 (Asthmatic Subjects)

Any subject requiring treatment for bronchoconstriction will have their FEV_1 monitored frequently until their FEV_1 has returned to within 90% of their baseline value or to a level considered acceptable by the investigator.

Any subject who does not respond adequately as per the investigator's judgment to treatment with bronchodilators will be withdrawn from the IMP and from further sputum induction attempts. Site SOPs will be followed at all times.

8.11.11. Additional Safety Procedures

Additional non-invasive procedures that are already specified in the protocol may be performed, if it is believed that an important effect of the IMP(s) is occurring or may occur at a time when no measurements are scheduled, or if extra procedures are needed in the interests of safety.

Additional blood samples for safety assessments may be taken if required by the investigator at any point.

8.11.12. Clinical Safety Laboratory Assessments

Available blood and urine sample results will be reviewed by a physician before the subject is dosed or receives their next dose, or is released from the study, as is appropriate.

A list of the laboratory parameters measured is presented in Appendix 2.

8.11.12.1. Haematology and Clinical Chemistry

Laboratory tests will be performed by the site's local laboratory according to the schedule of activities presented in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). Repeats are permitted on the day and/or on another day at the discretion of the investigator.

Site standard collection and processing procedures for blood samples will be adhered to throughout the study. Scheduled blood samples for clinical chemistry will be taken following at least an 8 hour fast (water is permitted).

8.11.12.2. SARS-CoV-2

SARS-CoV-2 testing will be performed by the site's local laboratory according to the schedule of activities presented in Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). Site standard collection and processing procedures for samples will be adhered to throughout the study.

8.11.12.3. Urinalysis

Urinalysis will be performed by the site's local laboratory according to site-specific SOPs according to the schedule of activities presented in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). Repeats are permitted on the day and/or on another day at the discretion of the investigator. Site standard collection and processing procedures for urine samples will be adhered to throughout the study.

8.11.12.4. Pregnancy Test

Pregnancy tests (serum test at screening [performed by site's local laboratory], on-site urine dipstick testing at all other time points will be performed for all female subjects, as detailed in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). Repeats are permitted on the day and/or on another day at the discretion of the investigator. Site standard collection and processing procedures for samples will be adhered to throughout the study.

8.11.12.5. Follicle-Stimulating Hormone Test

Serum FSH tests may be performed by the site's local laboratory for post-menopausal female subjects at the discretion of the Investigator to confirm post-menopausal status at screening. Site standard collection and processing procedures for blood samples will be adhered to throughout the study.

8.11.12.6. Drug Screen and Urine Cotinine

A urine drug screen, including urine cotinine, will be performed on-site using a dipstick method according to the schedule of activities presented in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). Repeats are permitted on the day and/or on another day at the discretion of the investigator. Site standard collection and processing procedures for urine samples will be adhered to throughout the study. Subjects will be screened for the drugs of abuse listed in Appendix 2.

8.11.12.7. Alcohol Breath Test

An alcohol breath test will be performed according to the schedule of activities presented in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3). Repeats are permitted on the day and/or on another day at the discretion of the investigator. A confirmed positive result will exclude the subject from screening or dosing during admission.

8.11.12.8. Abnormal Laboratory Findings

In cases where laboratory findings are outside the normal range and the investigator believes that the results may be of clinical significance, repeat sampling may be requested as clinically indicated. If the abnormal finding is clinically significant, appropriate actions will be taken e.g. the subject will not be entered into the study or the subject may be withdrawn from the study. The subject will be referred to their GP or other appropriate provider for further care. The same will apply if the results of the HBsAg, HCV Ab or HIV test are positive and in addition the investigator will ensure that adequate counselling is available if requested.

Abnormal results at follow-up assessments will also require repeat testing if the investigator believes the results may be of clinical significance.

Any clinically significant abnormality, including changes from baseline, must be reported as an AE.

Additional blood and/or urine samples may be taken for safety tests. Furthermore, additional assays outside those specified in the protocol may be performed for safety reasons as requested by the investigator.

8.12. Adverse Events and Serious Adverse Events

The definition of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study IMP/s, DPI (RS01) or study procedures, or that caused the participant to discontinue IMP (see Section 7.1).

8.12.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the follow-up phone call (Section 1.2).

All SAEs will be recorded and reported to the sponsor’s Drug Safety Unit and Medical Monitor immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study IMP/s or study participation, the investigator must promptly notify the sponsor.

8.12.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.12.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and AESIs will be followed until resolution, stabilisation, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 3.

8.12.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of the IMP under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Independent Ethics Committees (IEC), and investigators.
- For all studies, except those utilising medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g. summary or listing of SUSARs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IEC, if appropriate according to local requirements.

8.12.5. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after first dose of IMP and until 30 days after the last dose as outlined in Appendix 4.
- If a pregnancy in a female subject or the partner of a male subject is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 3.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.12.6. Cardiovascular and Death Events

Voriconazole has been associated with QTc interval prolongation. There have been rare cases of torsade de pointes in patients taking voriconazole, who also had risk factors such as cardiomyopathy.

Voriconazole should be administered with caution to patients with predisposing cardiac related problems and also with concomitant therapy which is known to prolong QTc interval. Additionally, any patients taking medications that are known to prolong QTc interval will be excluded from the study.

8.12.7. Adverse Events of Special Interest

An AESI is an adverse event of scientific and medical interest specific to the understanding of the investigational product and may require close monitoring and collecting additional information by the investigator. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterise and understand them in association with the use of this investigational product.

Adverse events of special interest (AESIs) with onset after the dosing (Day 1) to end of the safety follow-up period will be recorded.

The following adverse events of special interest (AESIs), that may occur and will be monitored during the study.

1. Respiratory Events:
   Moderate or severe dyspnoea/wheeze,

Moderate or severe cough,
Moderate or severe bronchospasm

2. Moderate or severe visual impairment/hallucination
3. Anaphylaxis and severe allergic reaction
4. Hepatotoxicity ≥3XULN for AST, ALT and bilirubin.

8.13. Treatment of Overdose

There is no antidote for voriconazole. In the advent of an adverse reaction, supportive and symptomatic treatment is indicated relevant to the clinical scenario. In serious cases subjects should be hospitalised for observation and/or further intervention as necessary.

8.14. Pharmacokinetics

8.14.1. Pharmacokinetic Blood Sampling

Venous blood samples will be withdrawn via an indwelling cannula or by venepuncture according to the schedule of activities presented in Section 1.2.1 (Part 1), Section 1.2.2 (Part 2) and Section 1.2.3 (Part 3).

Samples will be collected into appropriate tubes as specified by the bioanalytical laboratory. Site standard collection and processing procedures for blood samples will be adhered to throughout the study.

Serum samples will be shipped to Alderley Analytical for the analysis of voriconazole, and N-oxide voriconazole.

Samples will be analysed according to a validated method. Analytical methods are validated according to internationally accepted standards. The quality and integrity of the analytical work generated in this study will be evaluated in accordance with the study plan, validated method and SOPs of Alderley Analytical.

8.14.2. Induced Sputum Sampling (Part 2 and Part 3 only)

Induced sputum samples will be collected according to the time schedule presented in Section 1.2.2 and Section 1.2.3.

Samples will be collected into appropriate containers, as specified by the bioanalytical laboratory. Site standard collection and processing procedures for samples will be adhered to throughout the study.

Sputum samples will be shipped to Alderley Analytical for the analysis of voriconazole.

Samples will be analysed according to a validated method. Analytical methods are validated according to internationally accepted standards. The quality and integrity of the analytical work generated in this study will be evaluated in accordance with the study plan, validated method and SOPs of Alderley Analytical.

8.15. Biomarkers

Biomarkers are not evaluated in this study.

8.16. Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

Since the sample sizes for each study part are not statistically powered, there will be no formal hypothesis testing.

9.2. Sample Size Determination

.

Part 1 (SAD - Healthy subjects) and Part 2 (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 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.

9.3. Populations for Analyses

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

The Pharmacokinetic (PK) Concentration Set will consist of those subjects in the SAF who have at least one 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 serum PK parameter. Subjects will be analysed according to the treatment actually taken.

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

9.4. Statistical Analyses

This section describes the statistical methods that will be used to analyse the safety and PK parameters from study Parts 1, 2 and 3.

9.4.1. General considerations

For study parts 1 and 2, background and demographic characteristics and safety data will be summarised by ZP-059 dose and overall doses. PK data will be summarised by ZP-059 dose only.

For study part 3, background and demographic characteristics will be summarised by treatment sequence and overall. Safety and PK data will be summarised by treatment: Test (ZP-059) or Reference (oral voriconazole).

Full details of the statistical analyses will be provided in a separate statistical analysis plan (SAP), which will be finalised before database lock.

9.4.2. Background and Demographic Characteristics

Disposition, demographic data and other baseline characteristics (e.g. race, age, gender, ethnicity, weight and height) including medical history and prior/concomitant medication will be summarised as appropriate.

9.4.3. Safety Analysis

Adverse events (AEs) will be coded using the latest MedDRA dictionary version.

Incidence of treatment emergent adverse events (TEAEs) and incidence of TEAEs by system organ class (SOC) and preferred term (PT) will be presented as appropriate, with full detail provided in in the SAP.

Clinical laboratory, vital signs, ECG, pulmonary function and pulse oximetry parameters will be summarised as appropriate using summary statistics, with full detail provided in the SAP.

9.4.4. PK Analysis

The PK endpoints for statistical analysis, which will be assessed using serum concentrations for both voriconazole and N-oxide voriconazole are:

- Maximum observed serum concentration (Cmax)

- AUC Area under the serum concentration curve from zero to time of the last quantifiable concentration (AUC0-t), where t is 12 hours for Part 1, 24 hours for Part 2 and 96 hours for Part 3.
- Area under the serum concentration curve from zero extrapolated to infinity (AUC0-inf).

9.4.4.1. Dose proportionality

Dose proportionality will be assessed by fitting a power model as follows:

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

Where a value of 1 for β indicates perfect dose proportionality. Therefore, the estimate of β together with the corresponding 90% CI will be used to quantify dose proportionality. Dose proportionality will be assessed for each of the primary PK endpoint and 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.

9.4.4.2. Bioavailability

The PK endpoints estimated from Part 3 will be analysed to assess relative bioavailability of Test to Reference by fitting a mixed effects 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) (Test : Reference) 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 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.

9.4.4.3. PK Summaries

PK concentrations (including voriconazole concentrations in induced sputum) will be summarised and plotted over time. All PK parameters will also be summarised.

Further statistical analysis of other PK parameters and induced sputum concentrations may be performed. Full detail will be provided in the SAP.

9.5. Interim Analyses

No formal interim analyses are planned for this study. Details of interim safety data reviews to be performed are described in Section 6.6.

9.6. Data Monitoring Committee (DMC)

No data monitoring committee is planned for this study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
  - 20 July 2017 EMEA/CHMP/SWP/28367/07 Rev. 1 Committee for Medicinal Products for Human Use (CHMP) Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products
  - 21 July 2011 EMEA/CHMP/EWP/192217/2009 Committee for Medicinal Products for Human Use (CHMP) Guideline on bioanalytical method validation
  - London, 20 January 2010 Doc. Ref.: CPMP/QWP/EWP/1401/98 Rev. 1 Guideline on the investigation of bioequivalence"
  - https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19 guidance.
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IEC by the investigator and reviewed and approved by the IEC before the study is initiated.
- Any substantial amendments to the protocol will require IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC
  - Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, General Data Protection Regulation (GDPR), and the IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the subject performed any study procedures and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- An original signed ICF(s) must be provided to the subject or the subject's legally authorised representative.

Subjects who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by

the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

Data reviews during the study will be performed by the Safety Advisory Committee (SAC). See section 6.6 for details of the committee structure.

10.1.6. Dissemination of Clinical Study Data

A clinical study summary report will be provided to the appropriate IEC and results uploaded to EudraCT within one year of the end of the clinical study.

10.1.7. Data Quality Assurance

- All subject data relating to the study will be recorded on an electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion

unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in source data verification agreement (or equivalent).

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The first act of recruitment is the first site open and will be the study start date.

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs, the regulatory authorities, and any contract research organisation(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements

10.2. Appendix 2: Clinical Laboratory Tests

Haematology	Clinical Chemistry	Virology	Urinalysis	Urine Drugs of Abuse
Basophils Eosinophils Haematocrit (Packed Cell Volume- PCV) Haemoglobin Lymphocytes Mean Cell Haemoglobin (MCH) Mean Cell Haemoglobin Concentration (MCHC) Mean Cell Volume (MCV) Monocytes Neutrophils Platelet Count Red Blood Cell (RBC) Count White Blood Cell (WBC) Count	Alanine Aminotransferase (ALT) Albumin Alkaline Phosphatase Aspartate Aminotransferase (AST) Bicarbonate Bilirubin (Total) Bilirubin (Direct) (only if Total is elevated) Calcium Chloride Creatine Kinase (CK) Creatinine Follicle Stimulating Hormone (FSH; may be performed for post-menopausal female subjects to confirm post menopausal status at discretion of investigator) hCG (all female subjects) Gamma Glutamyl Transferase (GGT) Glucose Glucose (Fasting) Lactate dehydrogenase (LDH) Potassium Phosphate (Inorganic) Protein (Total) Sodium Urea	Hepatitis B Surface Antigen Hepatitis B Surface Antibody Hepatitis B Core Antibody Hepatitis C Virus Antibody Hepatitis C Virus RNA HIV Antibody Test for SARS-COV-2 (RT-PCR)	Bilirubin Blood Glucose hCG (all female subjects) Ketones Leukocytes Nitrites pH Protein Specific gravity Urobilinogen If urinalysis is positive for protein, blood, nitrite and/or leukocytes, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.	Amphetamines Barbiturates Benzodiazepines Cocaine Cotinine Marijuana/Cannabis Methadone Methamphetamine/ Ecstasy Morphine/ Opiates Phencyclidine Tricyclic Antidepressants

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of IMP, whether or not considered related to the study IMP. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalisation or prolongation of existing hospitalisation

- In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category

utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The relationship should be classified as follows:
  - **Not related**: a causal relationship between the study IMP and the AE is not a reasonable possibility
  - **Related**: a causal relationship between the study IMP and the AE is a reasonable possibility, and there are no other obvious causes for the AE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognised follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor via Paper Report Form

- Facsimile/E-Mail transmission of the SAE paper form is the preferred method to transmit this information to Zambon Drug Safety and the Medical Monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE form within the designated reporting time frames.
- Contacts for SAE reporting can be found on protocol page 3 (Zambon Drug Safety Unit and Medical Monitor contact details.

10.4. Appendix 4: Contraceptive Guidance, Exposure, Sperm Donation and Collection of Pregnancy Information

10.4.1. Contraception

Male subjects who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved method of effective contraception from the time of informed consent until 14 days after their last dose of IMP.

The following methods are acceptable:

Highly Effective Methods of Contraception (to be used by male subjects and their partners)

- Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  − oral
  − intravaginal
  − transdermal
- Progestogen-only hormonal contraception:
  − oral
  − injectable
  − implantable

- Intrauterine hormone-releasing system (IUS)

- Implantable intrauterine device (IUD)
- Surgical sterilisation (for example, vasectomy* or bilateral tubal occlusion/ligation)

*For vasectomy, the procedure should have been confirmed as successful and documentation made of this in the subject's notes.

Female subjects who are sexually active and of childbearing potential must use, an approved method of highly effective contraception from the time of informed consent until 30 days after their last dose of IMP.

Highly Effective Methods of Contraception (to be used by female subjects of childbearing potential)

- Combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  − oral

  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation*
  - oral
  - injectable
  - implantable

- IUS

- IUD
- Surgical sterilisation (for example, bilateral tubal occlusion/ligation)

*The following are not considered highly effective, i.e. not associated with inhibition of ovulation: Micronor, Norgeston, Noriday.

Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, they, with their partner, must comply with the contraceptive requirements detailed above.

Female subjects who are not of childbearing potential do not need to use any methods of contraception. A woman is considered of childbearing potential unless post-menopausal or permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, bilateral oophorectomy and bilateral tubal occlusion/ligation. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause (without hormone replacement therapy [HRT]). If required by the investigator, this may be confirmed by a follicle stimulating hormone (FSH) result of ≥40 IU/L.

10.4.2. Exposure to Partners during the Study

There is a risk of drug exposure through the ejaculate (which also applies to vasectomised males) that might be harmful to the sexual partners (both male and female), including pregnant partners of male subjects. Therefore, a condom should be used by all male subjects throughout the study and for 14 days after their last dose of IMP.

10.4.3. Sperm Donation

Male subjects should not donate sperm for the duration of the study and for at least 14 days after their last dose of IMP.

10.4.4. Collection of Pregnancy Information

Male subjects with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive IMP.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy after signature of a specific Informed Consent for Pregnancy Follow up. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered related to IMP by the investigator will be reported to the sponsor as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will be withdrawn from IMP. A male subject will be withdrawn from IMP in the event that his female partner becomes pregnant.

All pregnancies during the study will be reported to Zambon Drug Safety and the Medical Monitor (contact details on protocol page 3).

10.5. Appendix 5: Abbreviations

ABPA	Allergic Bronchopulmonary Aspergillosis
ADM	Admission
AE	Adverse Event
AESIs	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
AUC	Area Under the Serum Concentration-Time Curve
AUC_{0-t} the	Area under the Serum Concentration-Time Curve from Time Zero to Last Measurable Concentration
AUC_{0-inf}	Area Under the Serum Concentration-Time Curve from Time Zero to Infinity
AUC_{0-tau} the	Area Under the Serum Concentration-Time Curve from Time Zero to End of the Dosing Period
AUC_{tau} Dosing	Area Under the Serum Concentration-Time Curve to the End of the Interval
BID	Twice Daily
BMI	Body Mass Index
CCF	Congestive Cardiac Failure
CE-marked	Conformité Européene (European Conformity)
CF	Cystic Fibrosis
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
CL/F	Apparent Total Clearance of the Drug from the Serum
C_{max}	Maximum Serum Concentration
$C_{max,ss}$ Interval	Maximum Steady-State Serum Concentration During a Dosing
C_{min}	Minimum Serum Concentration
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organisation
$C_{ss,av}$ Dose	Average Steady-State Serum Drug Concentration During Multiple-Administration
C_{trough}	Trough Serum Concentration

CYP2C19	Cytochrome p450 2C19
CYP3A4	Cytochrome p450 3A4
DPI	Dry Powder Inhaler
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDV	Early Discontinuation Visit
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FEV_1	Forced Expiratory Volume in 1 Sec
FIH	First in Human
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
g	Grams
GCP	Good Clinical practice
GDPR	General Data Protection Regulation
GGT	Gamma Glutamyl Transferase
GLI	Global Lung Function Initiative
GMP	Good Manufacturing Practice
GMR	Geometric Mean Ratio
GP	General Practitioner
HB	Hepatitis B
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HCV Ab	Hepatitis C Virus Antibody
HIV	Human Immunodeficiency Virus
HIPAA	Health Insurance Portability and Accountability Act
HPMC	Hydroxypropyl Methylcellulose
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committees

Ig	Immunoglobulin
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL-4	Interleukin-4
IL-5	Interleukin-5
IMP	Investigational Medicinal Product
HPMC	Hydroxypropyl Methylcellulose
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
K_{el}	Apparent First-Order Terminal Elimination Rate Constant
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonists
LDH	Lactate Dehydrogenase
Log_e	Natural Logarithmic
MAD	Multiple Ascending Dose
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Cell Volume
Mg	Milligrams
MHRA	Medicines and Healthcare Products Regulatory Agency
MIC	Minimum Inhibitory Concentration
mL	Millilitres
msec	Millisecond
NOAEL	No-Observed-Adverse-Effect Level
RT-PCR	Reverse Transcription Polymerase Chain Reaction
PD	Pharmacodynamic
PEFR	Peak Expiratory Flow Rate
Ph. Eur	European Pharmacopoeia
PI	Principal Investigator
PIS	Participant Information Sheet
PK	Pharmacokinetic(s)
PKNCA	Pharmacokinetic Complete Noncompartmental analysis
PVC	Packed Cell Volume
QA	Quality Assurance
QD	Once Daily

QP	Qualified Person
Q.s	Quantum Satis
QTcF	QT Interval Corrected for Heart Rate Using Fridericia's Formula
R&D	Research and Development
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SABA	Short-Acting Beta-Agonists
SAC	Safety Advisory Committee
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAFS	Severe Asthma Associated with Fungal Sensitization
SAMA	Short-Acting Muscarinic Antagonist
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
SPF	Sun Protection Factor
Spp	Several Species
SQN	Syne Qua Non
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Elimination Half Life
TBD	To be Determined
TDL	The Doctor's Laboratory
Th2	T-helper Type 2
t_{max}	Time to Reach Maximum Serum Concentration
$t_{max,ss}$	Time to Reach Maximum Serum Concentration Following Drug Administration at a steady state
TP	Treatment Period
UK	United Kingdom
ULN	Upper Limit of Normal
Vz/F	Volume of Distribution During Terminal Phase After Non-Intravenous Administration
WBC	White Blood Cell
µg	Micrograms
% fluctuation	Percentage Fluctuation Over the Dosing Interval

% swing Percentage Swing Over the Dosing Interval

10.6. Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 01, Protocol Version 1.1: dated 14 February 2020:

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in this protocol amendment is to correct Typographical errors throughout.

Section # and Name	Description of Change	Brief Rationale
Appendix 10.4	Typographical errors corrected	'Highly' effective methods of contraception for males are to be followed to match inclusion criteria 4 (Part 1), inclusion criteria 6 (Part 2 & Part 3). Contraception option for 'Male condom with either female cap or diaphragm (double barrier) plus spermicide' removed from list for male subjects since this is not listed as a CTFG 'highly effective' method of contraception. IUS listed separately as a highly effective form of contraception for both male and female subjects, originally listed under progesterone only contraception in error

Section # and Name	Description of Change	Brief Rationale
Section 8.14.1, Section 9.3, Section 9.4.4, Section 10.5	Typographical errors corrected	Corrected to reflect the serum samples that are required for the serum PK analysis.

Protocol Version 1.0: dated 13 December 2019.

Original protocol.

11. References

1. Ashok Shah et.al (2016) Allergic Bronchopulmonary Aspergillosis: A Perplexing Clinical Entity; Allergy Asthma Immunol Res. 2016 Jul; 8(4): 282–297. Published online 2016 Mar 17. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4853505/

2. Agarwal, R.; Aggarwal, A.N.; Gupta, D.; Jindal, S.K. Aspergillus hypersensitivity and allergic bronchopulmonary aspergillosis in patients with bronchial asthma: Systematic review and meta-analysis. Int. J. Tuberc. Lung Dis. 2009, 13, 936–944.

3. Tracy MC, Okorie CUA, Foley EA, Moss RB. Allergic Bronchopulmonary Aspergillosis. J. Fungi 2016, 2, 17

4. LIVINGSTONE CHISHIMBA et.al (2012); Journal of Asthma, 2012; 49(4): 423–433; Voriconazole and Posaconazole Improve Asthma Severity in Allergic Bronchopulmonary Aspergillosis and Severe Asthma with Fungal Sensitization http://www.lifeworldwide.org/assets/uploads/files/Chishimba%20SAFS%20ABPA%20vori%20posa%20J%20Asthma%202012.pdf

5. O'Driscoll BR, Hopkinson LC, Denning DW. Mold sensitization is common amongst patients with severe asthma requiring multiple hospital admissions. BMC Pulm Med 2005; 5:4.

6. Moss RB. Treatment options in severe fungal asthma and allergic bronchopulmonary aspergillosis. Eur Respir J 2014; 43: 1487–1500

7. Stevens, D.A.; Schwartz, H.J.; Lee, J.Y.; Moskovitz, B.L.; Jerome, D.C.; Catanzaro, A.; Bamberger, D.M.; Weinmann, A.J.; Tuazon, C.U.; Judson, M.A.; et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N. Engl. J. Med. 2000, 342, 756–762.

8. Wark, P.A.B.; Hensley, M.J.; Saltos, N.; Boye, M.J.; Toneguzzi, R.C.; Epid, G.D.; Simpson, J.L.; McElduff, P.; Gibson, P.G. Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: A randomized controlled trial. J. Allergy Clin. Immunol. 2003, 111, 952–957

9. Tracy MC, Okorie CUA, Foley EA, Moss RB. Allergic Bronchopulmonary Aspergillosis. J. Fungi 2016, 2, 17

10. Wark, P.A.B.; Hensley, M.J.; Saltos, N.; Boye, M.J.; Toneguzzi, R.C.; Epid, G.D.; Simpson, J.L.; McElduff, P.; Gibson, P.G. Anti-inflammatory effect of itraconazole

in stable allergic bronchopulmonary aspergillosis: A randomized controlled trial. J. Allergy Clin. Immunol. 2003, 111, 952–957

11. Stevens, D.A.; Schwartz, H.J.; Lee, J.Y.; Moskovitz, B.L.; Jerome, D.C.; Catanzaro, A.; Bamberger, D.M.; Weinmann, A.J.; Tuazon, C.U.; Judson, M.A.; et al. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N. Engl. J. Med. 2000, 342, 756–762.

12. Agarwal R, Dhooria S, Sehgal IS, Aggarwal AN, Garg M, Saikia B, Behera D, Chakrabarti A. A Randomized Trial of Itraconazole vs Prednisolone in Acute-Stage Allergic Bronchopulmonary Aspergillosis Complicating Asthma. Chest 2018; 153(3):656-664

13. Tucker RM, Haq Y, Denning DW, Stevens DA. Adverse events associated with itraconazole in 189 patients on chronic therapy. J Antimicrob Chemother 1990; 26(4):561–566.

14. Richard B. Moss et.al (2014) Treatment options in severe fungal asthma and allergic bronchopulmonary aspergillosis; European Respiratory Journal 43: 1487-1500 https://erj.ersjournals.com/content/43/5/1487

15. Chishimba L et.al (2012); Journal of Asthma, 2012; 49(4): 423–433; Voriconazole and Posaconazole Improve Asthma Severity in Allergic Bronchopulmonary Aspergillosis and Severe Asthma with Fungal Sensitization

16. Felton T, Troke PF, Hope WW. Tissue penetration of antifungal agents. Clin Microbiol Rev. 2014 Jan; 27(1): 68–88.

17. Xing Y, Chen L, Feng Y, Zhou Y, Zhai Y, Lu J. Meta-analysis of the safety of voriconazole in definitive, empirical, and prophylactic therapies for invasive fungal infections. BMC Infect Dis. 2017; 17: 798.

18. Miao Q et.al (2019) Correlation of CYP2C19 genotype with plasma voriconazole exposure in South-western Chinese Han patients with invasive fungal infections. Medicine (Baltimore). 98(3):e14137. https://www.ncbi.nlm.nih.gov/pubmed/30653146

19. Patterson K, Strek E. Allergic Bronchopulmonary Aspergillosis. Proc Am Thorac Soc Vol 7. pp 237–244, 2010

20. Moss RB. Treatment options in severe fungal asthma and allergic bronchopulmonary aspergillosis. Eur Respir J 2014; 43: 1487–1500

21. Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, Moss R, Denning DW: Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. Clinical & Experimental Allergy, 2013 (43), 850-873.

22. Guidelines for Phase I Clinical Trials. Association of the British Pharmaceutical Industry Guidelines. London, UK; 2012 Edition (as amended 12 Nov 2014).

23. Chanez, P., Djukanovic, R., Ind, P.W., Holz, O., Maestrelli, P. & Sterk, P.J. (2002) Sputum Induction. *European Respiratory Journal,* **37**, 3-8. DOI: 10.1183/09031936.02.00000302

24. European Medicines Agency, 2017. Committee for Medicinal Products for Human Use (CHMP): *Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products*, EMEA/CHMP/SWP/28367/07 Rev. 1, London UK, 2017. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf

25. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Xaver Baur, Graham L. Hall, Bruce H. Culver, Paul L. Enright, John L. Hankinson, Mary S.M. Ip, Jinping Zheng, Janet Stocks and the ERS Global Lung Function Initiative, *Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations.* Eur Respir J 2012; 40: 1324–1343.