# Clinical Study Protocol

MR907-1501

## Title Page

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| **Protocol Title:** | A Phase 1, Multicentre, Open-Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of a Single IV Dose of Rezafungin Acetate in Paediatric Subjects from Birth to <18 Years of Age, Receiving Systemic Antifungals as Prophylaxis for Invasive Fungal Infection or to Treat a Suspected or Confirmed Fungal Infection |
| **Protocol Number:** | MR907-1501 |
| **Amendment Number:** | 3 |
| **Investigational Medicinal Product:** | Rezafungin acetate (MR907) |
| **Brief Title:** | Rezafungin Paediatric PK study |
| **Study Phase:** | 1 |
| **Regulatory Agency Identifier Number:** | EU CT number 2022-501985-23-00 |
| **Name and Address of the Sponsor:** | Mundipharma Research Ltd.<br>Unit 196, Cambridge Science Park, Milton Road,<br>Cambridge CB4 0AB, United Kingdom |
| **Sponsor Medical Monitor:** | Gu-Lung Lin, MD, DPhil<br>Mundipharma Research Ltd.<br>Unit 196, Cambridge Science Park, Milton Road,<br>Cambridge CB4 0AB, United Kingdom<br>Mobile: +44 (0) 7810 334530<br>Email: gu-lung.lin@mundipharma-rd.eu |
| **Version, Date:** | Version 4.0, 18 Jul 2023 |

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| **Good Clinical Practice (GCP) Statement** | This study will be performed in compliance with the principles of GCP and applicable local regulations. |

**PROTOCOL SIGNATURE PAGE – SPONSOR**

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

Mundipharma representative(s):

| Gu-Lung Lin, MD, DPhil | Senior Manager, Clinical Development |
|---|---|
| Print Name | Title |
| | |
| Signature | Date |

## APPROVAL

### Principal Investigator/Co-ordinating Investigator Signature Page

| | |
|---|---|
| **Study Title** | **A Phase 1, Multicentre, Open-Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of a Single IV Dose of Rezafungin Acetate in Paediatric Subjects from Birth to <18 Years of Age, Receiving Systemic Antifungals as Prophylaxis for Invasive Fungal Infection or to Treat a Suspected or Confirmed Fungal Infection** |
| **Protocol No.** | **MR907-1501** |
| **Version Date** | **18 Jul 2023** |
| **Version** | **4.0** |

I, the undersigned, have read and understood the Clinical Study Protocol (CSP) specified above and agree on its content. I agree to perform and conduct the clinical study as described in this CSP and in accordance with the Declaration of Helsinki, International Conference on Harmonisation (ICH) GCP, local applicable laws and regulations.

Name:

Signature:

Date:

**Protocol Amendment Summary of Changes**

| Document History | | |
|---|---|---|
| **Document** | **Date** | **Protocol Version Number** |
| Amendment 3 | 18 Jul 2023 | 4.0 |
| Amendment 2 | 26 May 2023 | 3.0 |
| Amendment 1 (UK) | 17 Apr 2023 | 2.0 (UK) |
| Amendment 1 | 16 Mar 2023 | 2.0 |
| Original Protocol | 16 Sep 2022 | 1.0 |

# 1 CLINICAL PROTOCOL SYNOPSIS

**Protocol Title:** A Phase 1, Multicentre, Open-Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of a Single IV Dose of Rezafungin Acetate in Paediatric Subjects from Birth to <18 Years of Age, Receiving Systemic Antifungals as Prophylaxis for Invasive Fungal Infection or to Treat a Suspected or Confirmed Fungal Infection

**Protocol Number:** MR907-1501

**Study Phase:** 1

**Sponsor:** Mundipharma Research Ltd.

**Study Rationale:** This study will assess the pharmacokinetics (PK), safety, and tolerability of a single intravenous (IV) dose of rezafungin in paediatric subjects from birth to <18 years who are receiving concomitant systemic antifungals as clinically indicated.

**Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To evaluate the pharmacokinetics (PK) of a single IV dose of rezafungin in paediatric subjects from birth to <18 years, receiving concomitant systemic antifungals as prophylaxis for invasive fungal infection (IFI) or to treat a suspected or confirmed fungal infection | Parts 1 and 2: The following PK parameters will be assessed:<br>$C_{max}$, $T_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, CL, $V_{ss}$, $V_z$, $t_{1/2}$<br><br>Part 3: Rezafungin plasma concentrations |
| **Secondary** | |
| To assess the safety and tolerability of a single IV dose of rezafungin in paediatric subjects from birth to <18 years, receiving concomitant systemic antifungals as prophylaxis for IFI or to treat a suspected or confirmed fungal infection | The safety evaluation will be based on clinical review of the following parameters:<br>• Incidence of treatment-emergent adverse events (TEAEs)<br>• Clinical laboratory evaluations (including haematology, blood chemistry and urinalysis)<br>• Vital signs<br>• 12-lead electrocardiograms (ECGs): clinically significant abnormalities<br>• Physical examination findings |

**Number of Subjects and Key Inclusion/Exclusion Criteria:**

It is planned to enrol 32 subjects (up to a maximum of 40 subjects [10 per age group] to achieve 32 subjects evaluable for primary analysis).

Eligible subjects will be enrolled into one of the following 4 age groups (8 patients planned per age group):

- Group 1 (12 to <18 years): 8 subjects
- Group 2 (6 to <12 years): 8 subjects
- Group 3 (2 to <6 years): 8 subjects
- Group 4 (birth to <2 years): 8 subjects

Subjects who are withdrawn from the study before completing all PK sampling may be replaced (up to 2 replacement subjects per group is allowed).

**Key Inclusion Criteria**
Male or female paediatric subjects from birth to <18 years of age who are receiving concomitant systemic antifungals (oral or IV) as prophylaxis for invasive fungal infection (IFI) or to treat a suspected or confirmed fungal infection.

**Key Exclusion Criteria**
History of anaphylaxis, hypersensitivity, or any serious reaction to the echinocandin class of antifungals and/or excipients of this formulation; Previous or current medical conditions of severe ataxia, persistent tremors, intracranial haemorrhage or neuropathy, or a diagnosis of epilepsy, multiple sclerosis, or a movement disorder (including, but not limited to, cerebral palsy and muscular dystrophy); Subjects with impaired renal or hepatic functions (alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal, conjugated bilirubin >24 µmol/L [1.4 mg/dL], serum creatinine >177 µmol/L [2 mg/dL], or receiving renal replacement therapy); Subjects with intestinal hypoxia, ischaemia, necrosis, or necrotising enterocolitis; Subject status is unstable (e.g., with sepsis or disseminated intravascular coagulation), and subject is unlikely to complete required study procedures; Participation in another interventional treatment trial with an investigational agent or presence of an investigational device at the time of informed consent or within 28 days preceding the informed consent.

**Summary of Study Design:**

This is a Phase 1, multicentre, open-label, single-dose study. The study will be conducted at approximately 10 sites across at least 3 countries in Europe.

The study will be conducted in 3 parts:

- Part 1 will include subjects aged 12 to <18 years (Group 1)
- Part 2 will include subjects aged 6 to <12 years (Group 2), and subjects aged 2 to <6 years (Group 3).

- Part 3 will include subjects from birth to <2 years (Group 4)

The study design for the 3 parts is similar and comprises a Screening (pre-treatment) period from Day -3 to Day -1, Dosing on Day 1 (single IV infusion of rezafungin) followed by multiple PK sampling, and a Follow-up visit on Day 30 (± 5 days) (Figure 1~~Figure 1~~, Table 1, Table 2). PK sampling will be performed at specified timepoints for each group.

**Part 1:** Subjects in Group 1 (12 to <18 years) will be dosed first. For this group, the formulation to be used will be same as the one used in the adult clinical trials at a dose of 3 mg/kg (not to exceed a total dose of 200 mg). PK sampling will be performed at the following 5 timepoints: at end-of-infusion ± 15 minutes, and thereafter between 3 and 4 hours after start of the infusion, between 6 and 8 hours after start of the infusion, at 48 hours (± 4 hours) after start of the infusion (Day 3), and at 168 hours (± 12 hours) after start of the infusion (Day 8). The exact date and time of the PK samples must be recorded.

An interim review of safety and PK data will be conducted by the Data Safety Monitoring Board (DSMB) after completion of Group 1. The data will be reviewed by the DSMB to ensure that exposure achieved in the subjects from this group is safe and well tolerated. This will allow for a decision to proceed to Part 2.

In parallel to this study a formulation development programme is being undertaken to identify a paediatric specific formulation for use in subjects <12 years of age. Once the paediatric formulation is available for use, after completion of Part 1, the study will be paused and a substantial amendment will be submitted to enable use of the paediatric formulation in Part 2 and Part 3 (for dosing in subjects <12 years of age).

**Part 2:** Enrolment for Group 2 and Group 3 will commence after safety has been confirmed by the DSMB and the paediatric formulation has been identified and ready to be used. The planned dose in these age groups is 4 mg/kg (not to exceed a total dose of 200 mg). The PK sampling timepoints for Part 2 will be the same as that dosefor Part 1: at endofinfusion ± 15 minutes, and thereafter between 3 and 4 hours after start of the infusion, between 6 and 8 hours after start of the infusion, at 48 hours (± 4 hours) after start of the infusion (Day 3), and at 168 hours (± 12 hours) after start of the infusion (Day 8). The dose and PK sampling timepoints may be adjusted as appropriate after assessment of the PK and safety data of Part 1.

A second interim review of safety and PK data will be performed when data from 50% of the subjects enrolled in Part 2 (Group 2 and Group 3) are available. The dose and PK sampling timepoints may be adjusted as appropriate after review of the PK and safety data (DSMB review 2). After completion of Groups 2 and 3; there will be another interim DSMB review (DSMB review 3) of the safety, tolerability, and PK data from the subjects in Groups 1, 2, and 3 (all subjects in Part 1 and Part 2).

A series of juvenile animal toxicity studies will be conducted in parallel with this PK study to investigate the effect of rezafungin on the growing and developing nervous system. Enrolment for Group 4 will not start until the juvenile animal toxicity studies are completed,

the animal safety data have been reviewed, and the safety and tolerability from the preceding parts have been confirmed by the DSMB.

**Part 3:** Subjects from birth to <2 years (Group 4) will be enrolled in Part 3. The planned dose for this age group is 5 mg/kg. Due to blood volume restriction, PK sampling will be done at only 3 timepoints for Group 4: at the end of infusion (± 15 minutes), at 24 hours (± 4 hours) after start of infusion, and at 168 hours (± 12 hours) after start of infusion. A maximum total of 1 mL of blood will be collected for PK sampling. The dose, PK sampling timepoints, extent of safety laboratory data required, and length of the Follow-up period may be adjusted as appropriate after review of the PK and safety data from Part 1 and Part 2 (DSMB review 3).

**Investigational Medicinal Product:** Rezafungin acetate (MR907)
Rezafungin is a sterile product of lyophilised powder for reconstitution with sterile water for injection prior to dilution into infusion bags containing normal saline, half-normal saline, or 5% dextrose. Each single-dose vial contains rezafungin acetate (200 mg of active rezafungin).

Dose: The dose for Group 1 is 3 mg/kg (not to exceed a total dose of 200 mg). The planned dose for both Group 2 and Group 3 is 4 mg/kg (not to exceed a total dose of 200 mg), and for Group 4, the planned dose is 5 mg/kg. However, the doses for Groups 2, 3, and 4 will be confirmed after a review of the interim PK and safety data from the preceding part(s) by the DSMB (DSMB review 1 and review 3). The dose may be adjusted as appropriate after the review.

Mode of administration: IV infusion over 2 hours (± 5 minutes).

**Reference Product:** Not applicable

**Treatment Duration:** This is a single-dose study. Subjects will receive a single IV infusion of rezafungin over a period of 2 hours (± 5 minutes).

**Statistical Methods:** In general, continuous data will be summarised by group using the descriptive statistics. Categorical data will be summarised by group as the number and percentage of subjects in each category.

Baseline is defined as the last value prior to the IV infusion of rezafungin (Screening).

**Sample Size:** No formal sample size calculation was performed. It is estimated that at least 8 subjects per age range will enable estimation of rezafungin PK in subjects from birth to <18 years of age.

**Data Analyses:**

Pharmacokinetic analysis:
The following PK parameters will be derived for subjects in Groups 1 to 3 only:

- $C_{max}$ Maximum observed plasma concentration
- $t_{max}$ Time at which the maximum plasma concentration was observed
- $AUC_{0-t}$ Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
- $AUC_{0-\infty}$ Area under the plasma concentration-time curve from time 0 extrapolated to infinity
- $t_{1/2}$ Terminal elimination half-life
- $\lambda_z$ Terminal elimination rate constant
- CL Total clearance
- $V_{ss}$ Volume of distribution at steady-state
- $V_z$ Apparent volume of distribution during the terminal phase

For subjects in Group 4, the plasma concentrations of rezafungin will be summarised using descriptive statistics.

All subjects who receive the single IV infusion of rezafungin and provide at least one blood sample for measurement of rezafungin plasma concentration will be included in the PK analysis set. The PK analysis set will be used for PK analysis.

Individual and mean plasma concentrations of rezafungin at each sampling timepoint will be presented by listings and descriptive statistics including: n, mean, standard deviation (SD), standard error (SE), geometric mean, coefficient of variation expressed as percent (CV%), median, minimum and maximum, as well as quartiles (Q1 and Q3).

All PK parameters will be calculated by non-compartmental analysis and detailed analysis will be included in the Statistical Analysis Plan.

The PK data from all groups may also be analysed using nonlinear mixed-effects modelling. Any PK modelling will be subject to a separate analysis plan and will be reported separately from the clinical study report for this study.

Safety Analysis

The Safety Analysis Set (i.e., all subjects who have received any amount of rezafungin) will be used for the analysis of safety data.

Safety will be evaluated through treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), clinical laboratory, vital signs, electrocardiogram (ECG), and physical examination findings. TEAEs are defined as adverse events (AEs) with an onset on or after administration of the investigational product (IP; rezafungin) until the Follow-up.

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of subjects experiencing TEAEs will be summarised by group, severity, and relation to IP. Treatment-emergent adverse events will be summarised by MedDRA System Organ Class and Preferred Term. The number and percentage of subjects reporting at least one TEAE will be summarised for each group (Groups 1, 2, 3, and 4), and overall. All AEs will be listed by subject.

Clinical laboratory data to be summarised include haematology, blood chemistry, and urinalysis. Laboratory data will be converted to International System of Units for reporting and processing purposes. Absolute values and changes from baseline will be presented descriptively. Laboratory data outside the reference ranges will be flagged, and clinical significance of the laboratory value change will be stated. Vital signs and 12-lead ECG data will be summarised by group and listed by subject. The number and percentage of subjects with clinically significant ECG findings will be summarised by group for each time-point. A summary of abnormal physical examination findings by group and scheduled visit (Study day) will be presented.

**Interim Analysis**

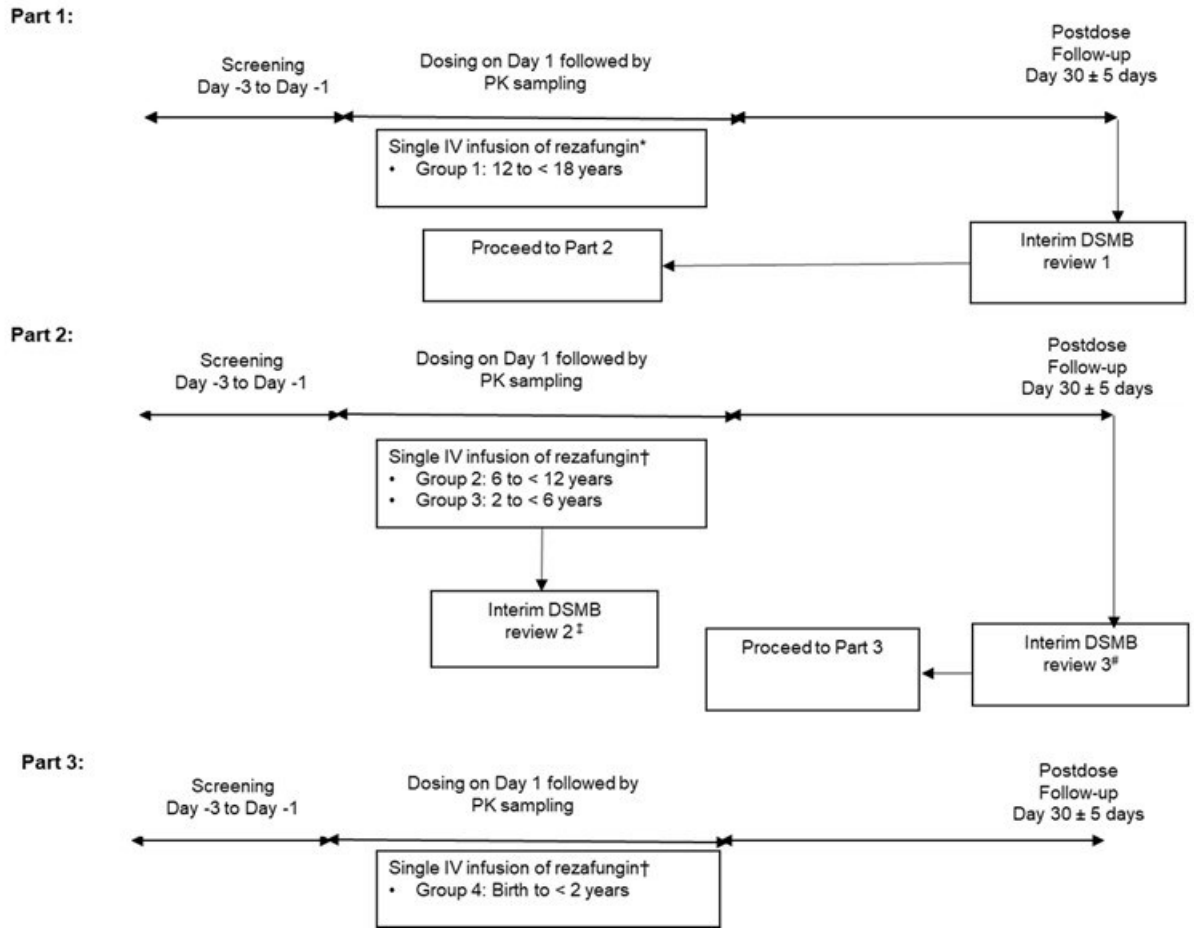
No formal interim analysis is planned for this study.

A DSMB has been appointed for this study to monitor the safety. Three interim reviews by the DSMB are planned during the study: The first interim review will be performed after completion of Part 1 (Group 1). The enrolment for Part 2 (Group 2 and Group 3) will commence only after DSMB review of Group 1 data and a decision to go ahead.

A second interim review by the DSMB is planned when data from 50% of the subjects enrolled in Part 2 are available.

A third DSMB review will be performed when Part 2 is completed. Enrolment for Part 3 (Group 4) will not start before review of safety and PK data from Part 1 and Part 2 is complete.

**Figure 1 Study Schema**




DSMB=Data Safety Monitoring Board; IV=intravenous; PK=pharmacokinetic
*Adult formulation; † paediatric formulation; ‡ DSMB review 2 to be held when 50% data from Group 2 and Group 3 are available; # Interim DSMB review 3: Interim review of safety and PK data of all subjects from Part 1 and Part 2 (Groups 1, 2 and 3).

**Table 1 Schedule of Assessments for Part 1 (Group 1: 12 to <18 Years) and Part 2 (Group 2: 6 to <12 Years; and Group 3: 2 to <6 Years)**

| **Study Period** | **Screening** | **Dosing** | | **PK Sampling Postdose** | | | | | **Follow-up / ET[a]** |
|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -3 to Day -1** | **Day 1** | | **Day 1** | | | **Day 3** | **Day 8** | **Day 30 ± 5 Days** |
| **Procedure** | | Predose | Single IV infusion of rezafungin | end-of-infusion ± 15 mins | Between 3 and 4 hrs after start of infusion | Between 6 and 8 hrs after start of infusion | 48 hrs ± 4 hrs after start of infusion | 168 hrs ± 12 hrs after start of infusion | |
| Informed consent/assent for minors[b] | x | | | | | | | | |
| Assess inclusion/exclusion criteria | x | | | | | | | | |
| Demography (age, sex, and race) | x | | | | | | | | |
| Baseline characteristics (height, weight, BMI*, and disease characteristics [indication for antifungal prophylaxis/treatment]) | x | | | | | | | | |
| Hospitalisation status at Screening (general ward/ICU)[c] | x | | | | | | | | |
| Medical/surgical history and current medical conditions | x | | | | | | | | |
| Prior and concomitant medication use[d] | x | x | x | x | x | x | x | x | x |
| Physical examination[e] | x | x | x | x | x | x | x | x | x |

| **Study Period** | **Screening** | **Dosing** | | **PK Sampling Postdose** | | | | | **Follow-up / ET[a]** |
|---|---|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -3 to Day -1** | **Day 1** | | **Day 1** | | | **Day 3** | **Day 8** | **Day 30 ± 5 Days** |
| **Procedure** | | Predose | Single IV infusion of rezafungin | end-of-infusion ± 15 mins | Between 3 and 4 hrs after start of infusion | Between 6 and 8 hrs after start of infusion | 48 hrs ± 4 hrs after start of infusion | 168 hrs ± 12 hrs after start of infusion | |
| Vital signs (temperature, pulse rate, respiratory rate, and blood pressure)[f] | x | x | x[f] | x[f] | x | x | x | x | x |
| Clinical laboratory tests (haematology, biochemistry, urinalysis)[g] | x | | | | | | | | x |
| Urine pregnancy test for postmenarchal females | x | | | | | | | | x |
| 12-lead ECG[h] | x | | | | x | | | | |
| IP administration[i] | | | x | | | | | | |
| Continuous vital sign and ECG monitoring (only during IP infusion)[j] | | | x | | | | | | |
| PK Sampling (venous or arterial samples)[k] | | | | x | x | x | x | x | |
| AE/SAE monitoring | | | x | x | x | x | x | x | x |
| Infusion-related reaction monitoring (collected as AEs) | | | x | x | x | x | | | |

AE=adverse event; BMI=body mass index; ECG=electrocardiogram; ET=early termination; ICU=intensive care unit; IP=investigational product; IV= intravenous; PK=pharmacokinetics; SAE=serious AE.

Note: When coinciding with each other, ECGs, vital signs, and pharmacokinetic blood collections should be performed in said order.

* BMI=kg/$m^2$ where kg is a subject's weight in kilograms and $m^2$ is their height in metres squared (Appendix 6).

a. ET assessments can be performed at the time of discontinuation. In case of ET, the reason for discontinuation must be documented.
b. Written parental (or appropriate legal representative) informed consent and/or age-appropriate assent/consent.
c. Record whether the subject is in the general ward or ICU. If the subject is in the ICU, record the Paediatric Index of Mortality 2 (PIM2) variables (Appendix 7).
d. All medication taken up to 7 days prior to the informed consent, medication ongoing after the informed consent, and all medication given to the subjects during the study until Follow-up (Day 30 ± 5 days) must be recorded.
e. A complete physical examination is to be performed at Screening and Follow-up. At all other time points, a brief targeted examination is to be performed as clinically indicated, driven by the subject's symptoms and signs. A complete and brief targeted physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and central and peripheral neurological systems.
f. Vital signs will be taken after subject is sitting or supine for at least 5 minutes and will include temperature, pulse rate, respiratory rate, and blood pressure. On the day of dosing (Day 1) vital signs will be taken predose, 15-30 minutes after the start of IP infusion, and 30-60 minutes after the completion of IP infusion.
g. Clinical laboratory tests (haematology, biochemistry, urinalysis): The following tests will be performed at Screening and at Follow-up: Complete blood count, alkaline phosphatase (ALP), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and conjugated bilirubin, creatinine, total protein and albumin, glucose (fasting or non-fasting), potassium, sodium, calcium (see Appendix 2 for details).
h. 12-lead ECG: at Screening and between 3 and 4 hours after start of IP infusion on Day 1.
i. The IP will be administered as a single IV infusion over a period of 2 hours (± 5 minutes). The formulation used for Group 1 will be same as the one used in the adult clinical trials. For Group 2 and Group 3, a paediatric specific formulation that is currently under development will be used.
j. Continuous vital sign and ECG monitoring will begin with start of IP infusion until completion of infusion.
k. PK blood samples will be collected at the following 5 timepoints: at end-of-infusion ± 15 minutes, then between 3 and 4 hours after start of infusion, between 6 and 8 hours after start of infusion, at 48 hours (± 4 hours) after start of infusion (Day 3), and at 168 hours (± 12 hours) after start of infusion (Day 8). In cases where a subject is discontinued before all PK samples have been collected (Day 8), a last PK sample may be collected at the time of discontinuation if the subject and/or his/her parent(s)/legally authorised representative consents. The exact date and time of the PK samples must be recorded.

**Table 2 Schedule of Assessments for Part 3 (Group 4: birth to <2 Years)**

| **Study Period** | **Screening** | **Dosing** | | **PK Sampling Postdose** | | | **Follow-up / ET[a]** |
|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -3 to Day -1** | **Day 1** | | **Day 1** | **Day 2** | **Day 8** | **Day 30 ± 5 Days** |
| **Procedure** | | Predose | Single IV infusion of rezafungin | end-of-infusion ± 15 mins | 24 hrs ± 4 hrs after start of infusion | 168 hrs ± 12 hrs after start of infusion | |
| Informed consent (parental consent/LAR)[b] | x | | | | | | |
| Assess inclusion/exclusion criteria | x | | | | | | |
| Demographics (age, sex, race, gestational age, and birth weight) | x | | | | | | |
| Baseline characteristics (height, weight, and disease characteristics [indication for antifungal prophylaxis/treatment]) | x | | | | | | |
| Hospitalisation status at screening (general ward/ICU)[c] | x | | | | | | |
| Medical/surgical history and current medical conditions | x | | | | | | |
| Prior and concomitant medication use[d] | x | x | x | x | x | x | x |
| Physical examination[e] | x | x | x | x | x | x | x |
| Vital signs (temperature, pulse rate, respiratory rate, and blood pressure)[f] | x | x | x[f] | x[f] | x | x | x |

| **Study Period** | **Screening** | **Dosing** | | **PK Sampling Postdose** | | | **Follow-up / ET[a]** |
|---|---|---|---|---|---|---|---|
| **Study Day** | **Day -3 to Day -1** | **Day 1** | | **Day 1** | **Day 2** | **Day 8** | **Day 30 ± 5 Days** |
| **Procedure** | | Predose | Single IV infusion of rezafungin | end-of-infusion ± 15 mins | 24 hrs ± 4 hrs after start of infusion | 168 hrs ± 12 hrs after start of infusion | |
| Clinical laboratory tests (haematology, biochemistry, urinalysis)[g] | x | | | | | | x |
| 12-lead ECG[h] | x | | | | x | | |
| IP administration[i] | | | x | | | | |
| Continuous vital sign and ECG monitoring (only during IP infusion)[j] | | | x | | | | |
| PK Sampling (venous or arterial samples)[k] | | | | x | x | x | |
| AE/SAE monitoring | | | x | x | x | x | x |
| Infusion-related reaction monitoring (collected as AEs) | | | x | x | x | | |

AE=adverse event; ECG=electrocardiogram; ET=early termination; ICU=intensive care unit; IP=investigational product; IV= intravenous; LAR=legally authorised representative; PK=pharmacokinetics; SAE=serious AE.

Note: When coinciding with each other, ECGs, vital signs, and pharmacokinetic blood collections should be performed in said order.

a. ET assessments can be performed at the time of discontinuation. In case of ET, the reason for discontinuation must be documented.

b. Written parental (or appropriate legal representative) informed consent.

c. Record whether the subject is in the general ward or ICU. If the subject is in the ICU, record the Paediatric Index of Mortality 2 (PIM2) variables (Appendix 7)

d. All medication taken up to 7 days prior to the informed consent, medication ongoing after the informed consent, and all medication given to the subjects during the study until Follow-up (Day 30 ± 5 days) must be recorded.

e. A complete physical examination is to be performed at Screening and Follow-up. At all other time points, a brief targeted examination is to be performed as clinically indicated, driven by the subject's symptoms and signs. A complete and brief targeted physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and central and peripheral neurological systems.

f. Vital signs will be taken in supine position and will include temperature, pulse rate, respiratory rate, and blood pressure. On the day of dosing (Day 1) vital signs will be taken predose, 15-30 minutes after the start of IP infusion, and 30-60 minutes after the completion of IP infusion.

g. Clinical laboratory tests (haematology, biochemistry, urinalysis): The following tests will be performed at Screening and at Follow-up: Complete blood count, alkaline phosphatase (ALP), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and conjugated bilirubin, creatinine, total protein and albumin, glucose (fasting or non-fasting), potassium, sodium, calcium (see Appendix 2 for details). Glucose can be measured by point-of-care testing to minimise the blood volume taken for the clinical laboratory tests if the point-of-care glucose meter is calibrated regularly as per the site's standard operating procedure.

h. 12-lead ECG: at Screening and at 24 ± 4 hours after start of IP infusion (Day 2).

i. The IP will be administered as a single IV infusion over a period of 2 hours (± 5 minutes).

j. Continuous vital sign and ECG monitoring will begin with start of IP infusion until completion of infusion.

k. PK blood samples will be collected at the following 3 timepoints: at end-of-infusion ± 15 minutes, at 24 hours ± 4 hours (Day 2) after start of infusion, and at 168 hours ± 12 hours (Day 8) after start of infusion. In cases where a subject is discontinued before all PK samples have been collected (Day 8), a last PK sample may be collected at the time of discontinuation if the subject and/or his/her parent(s)/LAR consents. The exact date and time of the PK samples must be recorded. A maximum total of 1 mL of blood will be taken for PK sampling.

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# 3 INTRODUCTION

Rezafungin is a semi-synthetic echinocandin antifungal agent that is being developed to treat invasive candidiasis (IC) and as a single agent for prevention of invasive fungal disease (IFD) caused by *Candida* species (spp.), *Aspergillus* spp., and *Pneumocystis jirovecii* in patients undergoing allogeneic blood or bone marrow transplantation.

Additional details related to the pharmaceutical properties and mechanism of action of the investigational product (IP) are available in the rezafungin Investigator's Brochure (IB; Edition 10, dated 07 September 2021).[1]

Currently, rezafungin does not have a Marketing Authorisation in any country. Clinical studies are ongoing in the United States (US), Europe, Asia Pacific and South America.

In the US, rezafungin was granted Orphan Drug designation for the treatment of candidemia and IC infections caused by susceptible *Candida* spp. by the US Food and Drug Administration (FDA) on 08 February 2016.

It was also granted Orphan designation status in the EU by the European Medicines Agency (EMA) on 06 January 2021 for treatment of IC.

## 3.1 Therapeutic Area/Background

Invasive fungal disease is a cause of significant morbidity and mortality among recipients of allogeneic haematopoietic stem cell transplant and patients receiving cytotoxic chemotherapy for haematologic malignancies.[2] Three of the most common IFDs are IC, invasive aspergillosis, and *Pneumocystis* pneumonia. Antifungal agents are routinely used in high-risk patients to prevent IFDs as attributable mortality is high after infection becomes established.

Invasive candidiasis is a serious infection caused by *Candida* spp. This is the most frequently detected yeast in the human microbiome[3], and can cause widely disseminated and/or bloodstream infections.[4]

These serious and life-threatening infections represent a significant public health issue, particularly in highly vulnerable patient populations such as the elderly, postsurgical, critically ill, and other hospitalised patients with serious medical conditions.[5,6,7]

In addition, because of increasing resistance to existing antifungal drugs, there is an urgent need to develop new and more effective antifungal agents to treat these serious infections.[8,9,10,11,12] About 7% of bloodstream infections have been reported to be caused by drug-resistant *Candida* spp. in the US. Furthermore, cases of multidrug-resistant *C. auris* are increasing globally over the past few years, and this has been considered as a serious threat to public health.[13,14]

Invasive candidiasis is not an uncommon infection in newborns, with an incidence of 7% to 20% in critically ill neonates.[15] As birth weight decreases, the risk of IC progressively increases.

Additionally, extremely-low-birth-weight (birth weight <1000 grams) neonates are particularly susceptible to central nervous system (CNS) infection, with 50 to 64% of cases reported to display CNS symptoms early in the disease.[15] CNS involvement is associated with high mortality (30 to 60%), compared with a Day-30 all-cause mortality of 14.4% in a recent study including neonatal and paediatric populations (0 to ≤18 years) with candidemia.[16] Long-term complications, including neuromotor developmental disorders, chronic lung disease, and severe retinopathy of prematurity, have also been documented in preterm neonates with CNS candidiasis.[15]

## 3.2 Rationale for Conducting the Study

In children, echinocandins are first-line agents for the treatment of IC. The European Society of Clinical Microbiology and Infectious Diseases has given caspofungin and micafungin an A-I recommendation, and anidulafungin a B-II recommendation (however, this was prior to the approval of anidulafungin in children). Liposomal amphotericin B is an alternative first-line therapy in this population.[17]

Rezafungin exhibited a low clearance and long half-life ($t_{1/2}$) following intravenous (IV) administration across all animal species tested (mice, rabbits, rats, dogs, and non-human primates). In man, rezafungin also has a low clearance (~0.2 L/h) and a long $t_{1/2}$ of around 5 to 6 days.[1] This enables rezafungin to be dosed once weekly, achieving a high front-loaded exposure, which differentiates it from the marketed echinocandins (caspofungin, micafungin and anidulafungin), which have a shorter $t_{1/2}$ and are dosed daily.

To date, there are no clinical studies evaluating rezafungin in paediatric subjects. This study will assess the pharmacokinetics (PK), safety and tolerability of rezafungin in subjects from birth to <18 years of age who are receiving concomitant systemic antifungal treatment as standard-of-care.

This PK study is one of the clinical studies required to be conducted for rezafungin, to comply with the Decision of the EMA on the Paediatric Investigation Plan dated 03 January 2019 (EMEA-002319-PIP01-17), modified as of 24 June 2022 (EMEA-002319-PIP01-17-M02).

## 3.3 Benefit and Risk Evaluation

Safety of rezafungin has been evaluated in several nonclinical and clinical studies. Summaries of findings are located in the IB.

**Nonclinical Studies**

A series of nonclinical studies have been conducted to demonstrate the efficacy of rezafungin in various biological models and to support its safe IV dosing in humans. All pivotal nonclinical safety studies were conducted in facilities in the US. The studies were performed in accordance

with the US Department of Health and Human Services, Food and Drug Administration, United States Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies and as accepted by Regulatory Authorities throughout the European Union (Organisation for Economic Co-operation and Development Principles of Good Laboratory Practice [GLP]), Japan (Ordinance on GLP from the Ministry of Health, Labour, and Welfare), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement.

Biological samples were obtained in nonclinical PK studies and toxicokinetic samples from toxicology studies aimed at measuring rezafungin concentrations. Concentrations were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). For the PK studies, the methods were not validated due to the exploratory nature of the supported studies. For support of GLP toxicology studies, LC-MS/MS methods were developed and validated to measure rezafungin in plasma (with $K_3$EDTA [tri-potassium ethylenediaminetetraacetic acid] as anticoagulant) from rats and monkeys as part of toxicokinetic analyses. These methods were validated in accordance with the FDA Draft Guidance for Industry: Bioanalytical Method Validation (2013), and FDA Guidance for Industry: Bioanalytical Method Validation (2001), in a manner consistent with the principles outlined in the US Code of Federal Regulations Title 21 Part 58, GLP for Nonclinical Laboratory Studies.

Briefly, plasma samples (25 µL for rat and 50 µL for monkey and rabbit) were processed using a protein-precipitation extraction procedure followed by analysis. Rezafungin concentrations were calculated with a $1/x^2$ linear regression over a concentration range of 0.100 to 100 µg/mL using deuterated-rezafungin (d9-rezafungin) as an internal standard. The mass spectrometer was operated in the selected reaction monitoring mode under optimised conditions for detection of rezafungin and d9-rezafungin positive ions formed by electrospray ionisation. Method transfer validations were also completed for the rat and monkey plasma methods between different bioanalytical sites of the Contract Research Organisation (CRO). In addition, method validation was conducted in rat milk to support analysis of rat milk samples during rat reproductive toxicology studies.

Studies in the neutropenic mouse systemic candidiasis model show that rezafungin is efficacious when administered by either the IV, intraperitoneal or subcutaneous route across a wide range of doses.

Rezafungin was found to be protective when used as prophylaxis in neutropenic as well as immunocompetent mouse models when challenged with *Candida* spp., *Aspergillus* spp., and *Pneumocystis murina*. These data suggest that rezafungin may provide benefit as antifungal prophylaxis in patients with haematological diseases at risk for infection.[1]

In the safety pharmacology studies in rats, rezafungin was tested for effects on neurobehavioral, cardiovascular (hemodynamic and electrocardiographic), and respiratory functional endpoints. There were no clinically significant observations or statistically significant changes in neurobehavioral parameters or body temperatures that were attributed to administration of rezafungin when administered once every 3 days over one week by IV slow bolus to male rats at doses up to 45 mg/kg, nor were there changes in the gross behavioural, physiological, or neurological state of the animals.[1]

Overall, the pharmacodynamic and safety pharmacology profiles of rezafungin support its proposed indications for the treatment of candidemia/IC, and as prophylaxis for *Candida* infections, invasive aspergillosis and *Pneumocystis jirovecii* pneumonia.

Relative to the marketed echinocandins, good safety margins exist for the observed toxicities (6 to 9X), versus the predicted human therapeutic plasma level in patients. Unlike other echinocandins, no hepatotoxicity was observed with rezafungin. Testicular degeneration, a finding seen with micafungin in rats and dogs, was also seen in rats administered rezafungin, but not monkeys. Schwann cell phospholipidosis was observed in peripheral nerves but did not lead to adverse findings at any dose up to the no observed adverse effect level (NOAEL) over a 13-week dosing period in 2 independent studies in monkeys, and a 26-week dosing period in rats and monkeys. Tremors, which occurred in some monkeys sporadically over a 9-week period (generally starting >4 weeks after Day 1), reversed with no adverse neurohistopathology observed, whereas non-adverse Schwann cell phospholipidosis was still present after a 13-week recovery period. Additionally, the tremors observed during the blinded 26-week monkey study had similar incidence and severity between the treated animals and control animals. Therefore, it is considered that there is no apparent relationship of the minor tremoring seen in monkeys to the non-adverse Schwann cell phospholipidosis. It is important to note that during dosing, the animals received reconstituted rezafungin, without the additional dilution into 0.9% saline as will be done for patients.

Rezafungin was negative in a complete genotoxicity test battery and showed a minimal phototoxic response after multiple doses in rats.

Rezafungin had no effect on male or female fertility in rats or on embryo-foetal development in rats and rabbits and no effect on pre- and postnatal toxicity, maternal reproductive function, and offspring development. Measurable concentrations of rezafungin were found in dams and foetuses. Repeat doses of rezafungin did cause reversible testicular changes in rats, a finding also reported with micafungin.

Toxicology data generated so far support the repeat dose use of rezafungin in humans from adolescent age through to adults. All rats in the toxicology studies of 1 to 6 months duration were sexually mature from the start of dosing. All monkeys in the GLP and non-GLP studies of 1 to 6 months duration were young adults (i.e., adolescents) or sexually mature adults. Based on the nonclinical data and safety profiles in adult human studies, single and repeat doses of rezafungin is considered safe for administration to 12 to <18-year-old humans.

Drug-induced phospholipidosis is considered related to lysosomal storage. There are more than 50 drugs in clinical use that have been identified to induce phospholipidosis in vitro and/or in vivo, including drugs that are used in children for prolonged periods (e.g., propranolol).[18] There are also data suggesting that lysosomal acidification becomes less efficient with ageing, indicating there may be age-related differences in the sensitivity to the phospholipidosis-inducing effect.[19] The human nervous system undergoes a critical period of structural and functional growth and development between birth and 2 years of age. Between the ages of 2 and 18 years in humans there is a period of growth and functional maturation of the nervous system with refinement of sensorimotor control. The effects of phospholipidosis on

the growing and developing nervous system is not known, nor is it known if the sensitivity of the nervous system is different in children versus adults (with regard to phospholipidosis or tremors). Therefore, a series of juvenile animal toxicity studies will be conducted in parallel with this PK study to investigate the condition and effect of phospholipidosis. Until after the juvenile animal toxicity studies are completed, no single dose of rezafungin will be administered to <2-year-olds, and no repeat doses of rezafungin will be administered to 2 to <12-year-old paediatric subjects.

The rezafungin formulation contains polysorbate 80 (PS80) which is known to cause toxicity in paediatrics related to the $C_{max}$ of PS80 infusion. The Paediatric Committee's Formulation Working Group in EMA have set a dose limit of PS80 in paediatric formulations (3 mg/kg) based on once daily administration, but there are precedents showing that this dose limit can be modestly exceeded as long as the infusion rate of PS80 is below a certain threshold (0.15 mg/kg/min) and thereby avoiding toxicities related to $C_{max}$ of PS80. This dosing regimen was successfully used with anidulafungin. Therefore, in order to minimise PS80 effects, a formulation development programme is being undertaken to identify a paediatric specific formulation with an appropriate PS80 level for use in subjects <12 years of age and it will be administered at an infusion rate of PS80 below 0.15 mg/kg/min, a rate considered safe by the EMA. Furthermore, administration of rezafungin in this PK study is single dose only, which will further reduce the risk from PS80 infusion effects.

**Clinical Studies**

Rezafungin has been assessed in 8 Phase 1 studies (of these, 7 studies were in adult healthy volunteers and 1 was in adults with hepatic impairment), including a single ascending dose study, a multiple ascending dose study, a definitive QT study, a photosafety study, a hepatic impairment study, a radiolabelled mass balance, absorption, metabolism, and excretion study, and 2 drug-drug interaction studies, one Phase 2 study (STRIVE [NCT02734862]), and two Phase 3 studies (a Phase 3 study for treatment of candidemia and/or IC [ReSTORE {NCT03667690} – global study completed], and a Phase 3 study for prophylaxis of IFD in adults undergoing allogeneic blood and marrow transplantation [ReSPECT {NCT04368559} – ongoing]).

Single and multiple dose PK parameters of rezafungin have been determined in healthy adult subjects with approximately dose proportional increases in exposure over single dose range of 50 mg to 1400 mg, and multiple dose range of 100 to 400 mg. Rezafungin has a low clearance (~0.2 L/h), a long $t_{1/2}$ (around 5 to 6 days) and a volume of distribution approximately equal to total body water (~40 L). Elimination of rezafungin is primarily faecal as the parent compound, with less than 1% of the dose eliminated as the parent compound in the urine (Data on file).

Rezafungin, at a single supratherapeutic dose of 1400 mg, did not prolong the QT interval or have any clinically significant effect on other cardiac parameters, including heart rate, PR interval and QRS interval, compared to placebo. Postdose echocardiogram results were normal in all subjects, indicating no effect on cardiac contractility or ejection fraction.

Assessment of rezafungin as an inhibitor or inducer of a range of probe substrates for cytochrome P450 (CYP450) drug metabolising enzymes (CYP1A2, CYP3A, CYP2C8 and CYP2B6) and drug transporter proteins (P-gp, BCRP, OATP, OCT-1, OCT-2, MATE1 and MATE2) showed that rezafungin did not cause any clinically relevant interactions. The need for dose adjustments is considered unlikely for drugs that are substrates for these CYP450 enzymes and drug transporter proteins, when administered with rezafungin. Rezafungin also did not cause any clinically relevant drug-drug interaction when administered with tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax, which are commonly administered co-medications. Therefore, no dose adjustments are necessary when rezafungin is administered with these drugs. Overall, rezafungin has been assessed as having a low drug-drug interaction liability.

In subjects with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, the mean exposure of a 400 mg dose of rezafungin was reduced by approximately 30% compared to matched subjects with normal hepatic function. Rezafungin exposure was similar in subjects with moderate and severe hepatic impairment and did not change with increasing degree of hepatic impairment. As hepatic impairment did not have a clinically meaningful effect on rezafungin PK, dose adjustments in patients with hepatic impairment are not necessary.

The results of the photosafety study of rezafungin showed there was increased risk of phototoxicity to the skin classified as mild, and similar in intensity to the positive control, ciprofloxacin. As rezafungin may cause increased risk of phototoxicity, patients should be advised to avoid sun exposure and other sources of ultraviolet (UV) radiation without adequate protection during rezafungin treatment (including 7 days after the last administration of rezafungin).

The Phase 2 (STRIVE) safety and efficacy study (NCT02734862) was a multicentre, prospective, randomised, double-blind study of rezafungin (IV) versus caspofungin (IV) for treatment of subjects with candidemia and/or IC. This study had 3 groups. Subjects randomised to Group 1 received 400 mg of rezafungin on Day 1 and Day 8, with optional doses of 400 mg on Day 15 and Day 22. Subjects randomised to Group 2 received 400 mg of rezafungin on Day 1 and 200 mg on Day 8, with optional doses of 200 mg on Day 15 and Day 22. Subjects randomised to Group 3 received a 70 mg loading dose of caspofungin on Day 1, followed by 50 mg of caspofungin daily (with the option of oral step-down therapy with fluconazole), for a total of 14 to 28 days.

The primary efficacy outcome was overall success defined as mycological eradication and resolution of systemic signs attributable to candidemia and/or IC at Day 14. Secondary efficacy outcomes were overall success at Day 5, Day 28, and follow-up, mycological eradication at Day 5, Day 14, Day 28, and follow-up, clinical cure as assessed by the Investigator at Day 14, Day 28, and follow-up, and all-cause mortality (ACM) at Day 30. Safety was evaluated by adverse events (AEs) and ACM.

A total of 207 patients were enrolled, of which 183 were included in the microbiological intent-to-treat (mITT) population, defined as all patients with documented *Candida* infection who received any amount of study drug. Overall cure was achieved in 60.5% (46/76) patients from

Group 1 (rezafungin 400 mg group), 76.1% (35/46) patients from Group 2 (rezafungin 400/200 mg group), and 67.2% (41/61) patients from Group 3 (caspofungin group). Excluding those with indeterminate responses, overall cure rates were 69.7% for Group 1, 81.4% for Group 2, and 70.7% for Group 3.[20]

In the mITT population, the clinical cure as assessed by the Investigator at Day 14 was achieved in 69.7% (53/76) patients in Group 1, 80.4% (37/46) patients in Group 2, and 70.5% (43/61) patients in Group 3. The 30-Day ACM rates were 15.8% (12/76), 4.3% (2/46), and 13.1% (8/61) in Group 1, Group 2, and Group 3, respectively (Data on file).

There were no notable differences in treatment-emergent adverse events (TEAEs) across the study groups. Between the rezafungin groups, there were no dose-related patterns in study drug-related TEAEs, severe TEAEs, serious adverse events (SAEs), or related SAEs. Most AEs were mild or moderate in severity (Data on file). Rezafungin was found to be safe and efficacious in the treatment of candidemia and/or IC.

The pivotal Phase 3 trial ReSTORE (NCT03667690) was a multicentre, prospective, randomised, double-blind, double-dummy, efficacy and safety study of rezafungin (IV) versus caspofungin (IV) followed by optional oral fluconazole step-down therapy (in qualifying subjects) in subjects with candidemia and/or IC. Subjects were randomised in a 1:1 ratio to receive rezafungin as a 400 mg loading dose in Week 1, followed by 200 mg once weekly, for a total of 2 to 4 weeks, or caspofungin as a single 70 mg IV loading dose on Day 1 followed by caspofungin 50 mg IV once daily (with the option of oral step-down therapy with fluconazole) for a total treatment of 14 to 28 days.

The primary efficacy outcome was global cure (confirmed by the Data Review Committee) at Day 14 for the EMA, and ACM at Day 30 (-2 days) for the FDA. Global cure was determined from clinical response, mycological response, and radiological response (for qualifying subjects with IC).

Non-inferiority was demonstrated for the EMA primary efficacy outcome of global cure at Day 14 for rezafungin as compared with caspofungin. The percentage of subjects with a global cure at Day 14 were comparable between treatment groups (59.1% [55/93] for rezafungin subjects and 60.6% [57/94] for caspofungin subjects). The 95% confidence interval (CI) of the treatment difference from a stratified analysis was -14.9% to 12.7% for global response at Day 14.

Non-inferiority was also demonstrated for ACM at Day 30 (- 2 days) in the mITT Population – the primary efficacy outcome for the FDA. A total of 23.7% (22/93) of rezafungin subjects and 21.3% (20/94) of caspofungin subjects were deceased by Day 30 or had an unknown survival status (treatment difference = 2.4% [95% CI: -9.7% to 14.4%]).

Analysis of the safety data obtained in ReSTORE indicates that rates of TEAEs and SAEs were comparable between the rezafungin and caspofungin arms. There were no apparent imbalances between the treatment groups in System Organ Classes (SOCs) of AEs. Related SAEs were similar in number between the two groups. There were no laboratory abnormalities that were commonly associated with either study drug, though there were some imbalances in

the 2-grade increases in toxicity for liver function tests that favours rezafungin. Furthermore, there were no apparent differences noted between vital sign and ECG data among the treatment groups.

Two specific types of AEs were found to be associated with rezafungin in clinical trials: infusion-related reactions and phototoxicity. In ReSTORE, there were 2 cases of infusion intolerability associated with rezafungin dosing and one in the caspofungin arm. While an AE of sunburn was observed in one subject in the Phase 2 STRIVE study following prolonged exposure to the sun, no phototoxicity occurred in the ReSTORE study.[1]

Due to the findings of tremors in monkeys exposed to prolonged, high doses (9.2X the exposure to the proposed commercial dose in adults), close attention was paid to any neurologic AEs (i.e., ataxia, neuropathy, and tremor). These neurologic AEs were balanced between the rezafungin and caspofungin study groups, with 2 subjects having tremors in the rezafungin group (0 in the caspofungin group) and 2 subjects having neuropathy in the caspofungin group (0 in the rezafungin group). These 2 cases of tremors were mild in severity and reversible.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of rezafungin (based on the adult clinical trials) can be found in the IB.

**Summary of Benefit and Risk Evaluation**

As this is a single-dose study, there is no direct clinical benefit expected for the subjects who will participate in this study. The information obtained from this study will be used for the further clinical development of rezafungin in the paediatric population.

The risk of AEs is minimised by careful selection of doses and participants for the study, the relatively short duration (single dose) of IP exposure, lowered infusion rate, and the extent of safety monitoring incorporated into the study.

Rezafungin will be administered in combination with a polyene or an azole (use of concomitant echinocandins is not allowed) used as standard-of-care treatment for IC or as prophylaxis for IFD.

# 4 STUDY OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To evaluate the pharmacokinetics (PK) of a single IV dose of rezafungin in paediatric subjects from birth to <18 years, receiving concomitant systemic antifungals as prophylaxis for invasive fungal infection (IFI) or to treat a suspected or confirmed fungal infection | Parts 1 and 2: The following PK parameters will be assessed:<br>$C_{max}$, $T_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, CL, $V_{ss}$, $V_z$, $t_{1/2}$<br><br>Part 3: Rezafungin plasma concentrations |
| **Secondary** | |
| To assess the safety and tolerability of a single IV dose of rezafungin in paediatric subjects from birth to <18 years, receiving concomitant systemic antifungals as prophylaxis for IFI or to treat a suspected or confirmed fungal infection | The safety evaluation will be based on clinical review of the following parameters:<br>• Incidence of treatment-emergent adverse events (TEAEs)<br>• Clinical laboratory evaluations (including haematology, blood chemistry and urinalysis)<br>• Vital signs<br>• 12-lead electrocardiogram (ECG): clinically significant abnormalities<br>• Physical examination findings |

# 5 STUDY DESIGN

## 5.1 Overall Study Design

This is a Phase 1, open-label, multicentre study, to evaluate the pharmacokinetics, safety and tolerability of a single dose of rezafungin (administered as IV infusion) in paediatric subjects from birth to <18 years of age receiving concomitant systemic antifungals as clinically indicated.

The study will be conducted at approximately 10 sites across at least 3 countries in Europe.

It is planned to enrol 32 subjects (up to a maximum of 40 subjects [10 per age group] to achieve 32 evaluable subjects for primary analysis).

- Group 1 (12 to <18 years): 8 subjects
- Group 2 (6 to <12 years): 8 subjects
- Group 3 (2 to <6 years): 8 subjects
- Group 4 (birth to <2 years): 8 subjects

Subjects who are withdrawn from the study before completing all PK sampling may be replaced (up to 2 replacement subjects per group is allowed).

The study will be conducted in 3 parts:

- Part 1 will enrol subjects aged 12 to <18 years (Group 1)
- Part 2 will enrol subjects aged 6 to <12 years (Group 2), and subjects aged 2 to <6 years (Group 3)
- Part 3 will enrol subjects from birth to <2 years (Group 4)

The study design for the 3 parts is similar and comprises a Screening (pre-treatment) period from Day -3 to Day -1, Dosing on Day 1 (single IV infusion of rezafungin) followed by multiple PK sampling, and a Follow-up visit on Day 30 (± 5 days). PK sampling will be performed at specified timepoints for each group. See Figure 1~~Figure 1~~ for the study schema, and see Table 1 and Table 2 for the Schedule of Assessments (SoA).

**Part 1**

Subjects in Group 1 (aged 12 to <18 years) will be dosed first. For this group, the formulation to be used will be same as the one used in the adult clinical trials at a dose of 3 mg/kg (not to exceed a total dose of 200 mg).

For each participant, the study will consist of:

- Screening between Day -3 and Day -1
- Administration of a single IV infusion of rezafungin over 2 hours (± 5 minutes) on Day 1
- Blood sampling for PK measurements at the following timepoints: at end-of-infusion ± 15 minutes, and thereafter between 3 and 4 hours after start of infusion, between 6 and 8 hours after start of infusion, at 48 hours (± 4 hours) after start of infusion (Day 3), and at 168 hours (± 12 hours) after start of infusion (Day 8). The exact date and time of the PK samples must be recorded.
- A Follow-up visit on Day 30 (± 5 days)

After completion of the Follow-up visit for all subjects in Group 1, there will be an interim review of the safety, tolerability, and PK data. The data will be reviewed by the Data Safety Monitoring Board (DSMB) to ensure that the exposure achieved in subjects from this group is safe and well tolerated. This will allow for a decision to proceed to Part 2.

In parallel to this study a formulation development programme is being undertaken to identify a lower strength paediatric specific formulation with an appropriate PS80 level for use in subjects <12 years of age. A lower strength formulation (e.g., 100 mg/vial, compared with 200 mg/vial for the formulation used in Group 1) would reduce the risk of a 10-fold overdose in children with a weight of <3 kg. Once the paediatric formulation is available for use, after completion of Part 1, the study will be paused and a substantial amendment will be submitted to enable use of the paediatric formulation in Part 2 and Part 3 (for dosing in subjects <12 years of age).

**Part 2**

Enrolment for Part 2 (subjects aged 2 to <12 years) will commence after safety has been confirmed by the DSMB and the paediatric formulation has been identified and ready to be used. The dose for this age group is planned to be 4 mg/kg (not to exceed a total dose of 200

mg). The dose and PK sampling timepoints may be adjusted as appropriate after assessment of the PK and safety data of Part 1.

The study design and duration of Part 2 will be similar to that for Part 1: a 3-day Screening period, Dosing on Day 1 (a single IV infusion of rezafungin) followed by five PK samplings between Day 1 and Day 8, and a Follow-up visit on Day 30 (± 5 days).

In Part 2, subjects aged 6 to <12 years (Group 2) and 2 to <6 years (Group 3) will be enrolled in parallel. The PK sampling timepoints for Part 2 will be the same as that for Part 1: at end-of-infusion ± 15 minutes, and thereafter between 3 and 4 hours after start of the infusion, between 6 and 8 hours after start of the infusion, at 48 hours (± 4 hours) after start of the infusion (Day 3), and at 168 hours (± 12 hours) after start of the infusion (Day 8). After data from approximately 50% of the subjects aged 2 to <12 years are available, there will be a second interim review of the safety and PK data by the DSMB to ensure that the exposure achieved in subjects from this age group is safe and well tolerated, and inform whether adjustments to the dose and PK sampling timepoints are required for the remaining subjects. Recruitment/dosing will not be paused during this DSMB review.

After completion of Part 2, there will be another interim review (interim review 3) of the safety, tolerability, and PK data from the subjects in Groups 1, 2, and 3.

A series of juvenile animal toxicity studies will be conducted in parallel with this PK study to investigate the effect of rezafungin on the growing and developing nervous system. Enrolment for Group 4 will not start until the juvenile animal toxicity studies are completed, the animal safety data have been reviewed, and the safety and tolerability from the preceding parts have been confirmed by the DSMB.

**Part 3**

Subjects from birth to <2 years (Group 4) will be enrolled in Part 3. The planned dose for this age group is 5 mg/kg. Due to blood volume restriction, PK sampling will be done at only 3 timepoints for Group 4: at the end-of-infusion (± 15 minutes), at 24 hours (± 4 hours) after start of infusion (Day 2), and at 168 hours (± 12 hours) after start of infusion (Day 8). A maximum total of 1 mL of blood will be taken for PK sampling. The dose and PK sampling timepoints may be adjusted as appropriate after assessment of the PK and safety data of Part 1 and Part 2.

All subjects will be monitored for AEs and SAEs at timepoints specified in Table 1 and Table 2. Laboratory evaluations, electrocardiograms (ECGs), vital signs, and physical examinations will be performed at Screening and at timepoints specified in Table 1 and Table 2.

### 5.1.1 Recruitment

The recruitment process will be taking place in the inpatient hospital setting. The Investigators will identify potential subjects through review of the medical records and complete a participant identification and enrolment log before direct communication with the subjects and/or their parent(s)/legally authorised representative (LAR). This document will be reviewed by the Sponsor site contact for completeness.

The participant identification and enrolment log will be treated as confidential and will be filed by the Investigator in the study file. To ensure participant confidentiality, no copy will be made.

### 5.1.2 Informed Consent

Subjects and/or their parent(s)/LAR will sign the study specific informed consent form (ICF) prior to any study specific screening procedures being performed. The written informed consent/age-appropriate assent will be obtained from all subjects and/or their parent(s)/LAR, regardless of their eligibility for the study; the signed ICFs will be retained and archived at study site and another copy will be provided to the subject.

### 5.1.3 Screening

At Screening, eligibility of the subject to participate in the study will be determined by the Investigator based on the inclusion/exclusion criteria. Screening assessments will occur prior (Day-3 to Day-1) to rezafungin administration.

In cases where a participant does not meet the criteria for participation in this study (screen failure), the main reason for non-eligibility is to be documented in the electronic Case Report Form (eCRF).

The following Screening assessments will be performed within 3 days prior to dosing:

- Written parental (or LAR) informed consent and/or age-appropriate consent/assent (Note: no study procedures may be performed prior to obtaining written informed consent)
- Assess eligibility criteria
- Demographics: age, sex, and race (for Groups 1, 2, and 3: 2 to <18-years age group); age, sex, race, birth weight and gestational age (for Group 4: birth to <2-years age group)
- Baseline characteristics: height, weight, body mass index (BMI; only for Groups 1, 2, and 3 [Appendix 6]), and disease characteristics (indication for antifungal prophylaxis/treatment)
- Medical, surgical history and current medical conditions, including whether the subject is in the general ward or ICU. If the subject is in the ICU, record the Paediatric Index of Mortality (PIM2) variables (Appendix 7)
- Prior and concomitant medication use: All medication taken up to 7 days prior to signing the ICF and medication ongoing at study entry (after informed consent) must be recorded. Note: Antifungal medications that the subject was receiving prior to enrolment must be recorded (treatment with a non-echinocandin agent [either an azole or a polyene as standard-of-care] is allowed during the study). If a subject has previously received an echinocandin, and it has been changed to an alternative antifungal treatment (i.e., an azole or a polyene), he/she will be eligible for the study as long as there is a minimum of 5-day washout of the echinocandin, before the administration of rezafungin

- Complete physical examination: A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and central and peripheral neurological system
- Vital signs: Vital signs will be taken after subject is sitting or supine for at least 5 minutes and will include temperature, pulse rate, respiratory rate, and blood pressure (Appendix 5)
- Clinical laboratory tests: haematology, biochemistry, and urinalysis (see Appendix 2 for details)
- Urine pregnancy test (for postmenarchal females)
- 12-lead ECG

The Screening assessments will be considered as baseline assessments.

### 5.1.4 Dosing on Day 1 and Subsequent Pharmacokinetic Assessments

Subjects with suspected or confirmed fungal infection, or subjects who require prophylactic systemic antifungals who meet the eligibility criteria will receive a single IV infusion of rezafungin on Day 1 at a dose of 3 mg/kg (Group 1: 12 to <18 years) or 4 mg/kg (Group 2 and Group 3: 2 to <12 years) up to a maximum total dose of 200 mg, or 5 mg/kg (Group 4). The doses for Groups 2, 3, and 4 may be adjusted as appropriate after interim reviews of PK and safety data. Subjects will be continuously monitored (vital signs and continuous ECG monitoring) for the duration of infusion administration up to the end of the rezafungin infusion.

Assessments performed on Day 1 include:

- Record concomitant medications
- Brief targeted physical examination: A brief targeted physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and central and peripheral neurological system, driven by the subject's symptoms and signs
- Vital signs: Vital signs will be taken after subject is sitting or supine for at least 5 minutes and will include temperature, pulse rate, respiratory rate, and blood pressure (predose, 15 to 30 minutes after the start of drug administration, and 30 to 60 minutes after completion of the infusion)
- 12-lead ECG: at any time between 3 and 4 hours after start of IP infusion on Day 1 for Groups 1, 2, and 3. For Group 4, postdose ECG will be performed at 24 ± 4 hours after start of IP infusion (Day 2).
- Continuous vital sign and ECG monitoring: during infusion
- Blood sampling for PK measurement at end-of-infusion ± 15 minutes, then between 3 and 4 hours after start of infusion, and between 6 and 8 hours after start of infusion (for Groups 1, 2, and 3). PK sampling for Group 4 will be performed at the end-of-infusion (± 15 minutes).
- Record TEAEs/SAEs (including infusion-related reactions)

In addition to the above PK sampling timepoints, blood samples for PK measurement will also be collected at 48 hours (± 4 hours) after start of infusion (Day 3) and at 168 hours ± 12 hours (Day 8) after the start of rezafungin IV infusion for Groups 1, 2, and 3, and at 24 hours (± 4 hours) after start of infusion (Day 2), and at 168 hours (± 12 hours) after start of infusion (Day 8) for Group 4. The exact date and time of the PK samples must be recorded.

### 5.1.5 Follow-up or Early Termination

The Follow-up assessments will be performed on Day 30 (± 5 days) for all subjects. In case of subjects who withdraw consent before the Follow-up visit, or are discontinued early (for safety reasons) from the study, early termination (ET) assessments can be performed at the time of discontinuation. The reason for ET must be recorded in the eCRF. In cases where a subject is discontinued before all PK samples have been collected, a last PK sample can be collected if the subject and/or his/her parent(s)/LAR consents. The exact date and time of the PK sample must be recorded.

The following assessments will be performed at Follow-up or ET:

- Record concomitant medication use (includes medications that are ongoing or started after Day 1)
- Complete physical examination: A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and central and peripheral neurological system
- Vital signs: Vital signs will be taken after subject is sitting or supine for at least 5 minutes and will include temperature, pulse rate, respiratory rate, and blood pressure
- Clinical laboratory tests: haematology, biochemistry and urinalysis (see Appendix 2 for details)
- Urine pregnancy test (for postmenarchal females)
- Record TEAEs/SAEs (see Appendix 3)
- For ET, in addition to the above, reason for early termination must be recorded in the eCRF

## 5.2 Scientific Rationale for Study Design

This is the first study investigating the use of rezafungin in paediatric subjects.

The PK of a drug in the paediatric population usually cannot be precisely predicted from that in adults. Therefore, PK studies are needed to determine the appropriate paediatric dosing regimen.

This study has been designed to investigate the PK and safety of a single IV dose of rezafungin in paediatric subjects from birth to <18 years in combination with a polyene or an azole (use of concomitant echinocandins is not allowed) used as standard-of-care for treatment of suspected or confirmed fungal infection or as prophylaxis for IFD.

Given the age of the study participants a sparse PK sampling schedule has been selected to reduce the number of blood samples required by the subjects in the study. The plasma concentration data obtained from these samples will be used to develop a population PK model for paediatric subjects, to predict the exposure in children and confirm the dosing regimen for this population.

The study will be staggered to dose the 12 to <18 year olds first, followed by the 2 to <12-years age group, followed by birth to <2-years age group, respectively. Enrolment to Part 2, and subsequently to Part 3 of the study (i.e., the <12-years age groups) will start only after a review of the safety, tolerability and PK data of the preceding study Part(s) by the DSMB. This will enable confirmation of the dose and PK sampling timepoints planned for subjects <12 years old.

The primary objective of this study is to define the safety, tolerability and PK of rezafungin, as opposed to efficacy; therefore, the subjects in this study will also be receiving standard-of-care antifungal treatment. To aid recruitment into this study a decision was made to include subjects receiving systemic antifungals prophylactically as well as subjects receiving systemic antifungals to treat a suspected or confirmed fungal infection.

Non-adverse Schwann cell phospholipidosis was observed in peripheral nerves in rats and monkeys. Therefore, a series of juvenile animal toxicity studies will be conducted in parallel with this PK study to investigate the condition and effects of phospholipidosis on the growing and developing nervous system. Enrolment for Group 4 (from birth to <2 years) will not start until the juvenile animal toxicity studies are completed and the safety data have been reviewed.

### 5.3 Justification for Dose

The doses selected for this study are based on the output of population PK modelling and simulation. A population model has been developed for rezafungin using data obtained from healthy and hepatically impaired adult subjects from Phase 1 studies, and adult patients with candidemia and/or IC from the Phase 2 (STRIVE), and Phase 3 (ReSTORE) studies. The population model is a 3-compartment model with first-order elimination, and body surface area (BSA) and albumin concentrations were identified as two of the statistically significant covariates of rezafungin exposure (Data on file). Weight-based dosing (mg/kg) was selected for dose normalisation for the paediatric population. To simulate the exposure in the different paediatric age groups, for a range of weight-based dosing regimens (mg/kg), the adult model was used, along with estimates of BSA from the National Healthy and Nutritional Examination Survey (NHANES) data base, produced by the Centers for Disease Control and Prevention (CDC) in the US. In addition, the albumin distribution in adult patients from STRIVE and ReSTORE was used and values were sampled at random from this population.

The adult dosing regimen for commercialisation is an initial dose of 400 mg on Day 1 followed by a 200 mg dose on Day 8, and once weekly thereafter. The doses of rezafungin used in this study have been chosen to be similar to the single 200-mg adult dose on the basis of predicted plasma exposure. As this is a single-dose PK study and not an efficacy trial it is not necessary

to select an efficacious dose, but rather to ensure that the dose will be sufficient to enable PK assessment in the paediatric population.

Rezafungin will be administered as an IV infusion over a period of 2 hours. Using the paediatric population PK model, the dose for subjects aged 12 to <18 years has been selected as 3 mg/kg (not to exceed a total dose of 200 mg), and the dose for subjects aged 2 to <12 years is 4 mg/kg (not to exceed a total dose of 200 mg). The dose administered to Group 2 and Group 3 (children aged 2 to <12 years) will be confirmed after an interim review of the safety and PK data of Part 1 by the DSMB (DSMB review 1). Based on this review, the dose and PK sampling timepoints for Part 2 (Groups 2 and 3) may be adjusted as appropriate. The planned dose for subjects from birth to <2 years (Group 4) is 5 mg/kg. However, the dose and PK sampling timepoints for Group 4 may be adjusted as appropriate after assessment of the PK and safety data of Part 1 and Part 2 (DSMB review 3).

The formulation to be used for dosing Group 1 (12 to <18 year olds) is the formulation used in adult clinical trials. This formulation, however, contains PS80, which is known to cause toxicity in younger paediatric populations. To minimise the PS80 effects, in parallel to this study a formulation development programme is being undertaken to attempt to identify a lower strength paediatric specific formulation with an appropriate PS80 level for use in children <12 years of age. Once the paediatric formulation is available for use and after completing dosing Group 1 subjects, the study will be paused and a substantial amendment will be submitted to enable the paediatric formulation to be dosed to subjects in Groups 2, 3, and 4.

### 5.4 End-of-Study Definition

The end-of-study is defined as the last visit of the last subject in the study.

For an individual subject, the subject is considered to have completed the study if he/she has completed all visits per the SoA, including the Follow-up visit (see Table 1 and Table 2).

## 6 STUDY POPULATION

### 6.1 Inclusion Criteria

To be eligible for enrolment, a subject must fulfil all of the following inclusion criteria:

1. Male or female subjects from birth to <18 years of age
2. Provide written parental (or LAR) informed consent and/or age-appropriate informed consent/assent (per national regulations/guidance) prior to any study-related procedure
3. Subject has sufficient central or peripheral venous access to permit administration of study medication, collection of PK samples and monitoring of laboratory safety variables

4. For subjects ≥2 years of age, having a BMI (weight in kilograms divided by height in metres, squared) between the 2nd and 98th percentiles, inclusive (Appendix 6)
5. For a female subject who has undergone menarche and is considered to be of childbearing potential:
    - True abstinence OR utilises one of the following for at least 1 month prior to Screening: hormonal contraceptives (injectable, oral, patch, or vaginal ring), intrauterine device, or barrier method (diaphragm). This method must be used in combination with a barrier method of contraception for their male partner (condom). Subjects must be willing to practice these methods for at least 30 days after study drug administration (until Follow-up)

    ***Note***: a female subject is considered to be of childbearing potential if the subject is fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
6. For male subjects who are sexually active with female partners who have undergone menarche: subject must be using and willing to continue using medically acceptable forms of contraception (male condom for subjects plus an additional method of contraception for their female partners) from Screening and for at least 3 months after study drug administration
7. Currently receiving systemic antifungals (oral or IV) as clinically indicated either:
    - for suspected or confirmed fungal infection, OR
    - as prophylaxis for IFI

    ***Note***: In subjects who are receiving systemic antifungals for the treatment of suspected or confirmed fungal infection or as prophylaxis for IFI, rezafungin will be administered in addition to standard-of-care as per institutional, national, or international guidelines, as long as it involves a non-echinocandin agent (an azole or a polyene; subjects can receive only either an azole or polyene, not both). If a subject has previously received an echinocandin, and it has been changed to an alternative antifungal treatment (i.e., an azole or a polyene), he/she will be eligible for the study as long as there is a minimum of 5-day washout of the echinocandin, before the administration of rezafungin.
8. Subjects and parent(s)/LAR are willing and able to comply with the study instructions.

### 6.2 Exclusion Criteria

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

1. History of anaphylaxis, hypersensitivity, or any serious reaction to the echinocandin class of antifungals and/or excipients of this formulation, including, but not limited to, hereditary sugar disorders (e.g., fructose intolerance, sucrase-isomaltase deficiency), or echinocandin-induced exfoliative skin disorders (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis)

2. Subject has a concurrent medical condition that in the opinion of the Investigator and/or medical monitor precludes enrolment into the study
3. Evidence of impaired hepatic or renal functions, as defined by aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN), conjugated bilirubin >24 µmol/L (1.4 mg/dL), serum creatinine >177 µmol/L (2 mg/dL), or receiving renal replacement therapy
4. The Investigator anticipates the subject becoming anaemic and not tolerating blood draws during the study period
5. Subjects have intestinal hypoxia, ischaemia, necrosis, or necrotising enterocolitis
6. Neonates with hyperbilirubinaemia and requiring phototherapy
7. History of severe ataxia, persistent tremors (e.g., due to persistent hypoglycaemia, persistent hypocalcaemia, encephalopathy, etc.), intracranial haemorrhage, or neuropathy, or a diagnosis of epilepsy, multiple sclerosis, or a movement disorder (including, but not limited to, cerebral palsy and muscular dystrophy), any of which is of Grade 2 or higher, based on the Division of Acquired Immunodeficiency Syndrome (DAIDS) criteria, Version 2.1
8. Planned or ongoing therapy at Screening or during the course of the study with a known severe neurotoxic medication (see Appendix 4) or CNS irradiation, or with a known moderate neurotoxic medication in a subject with ataxia, persistent tremors, intracranial haemorrhage, motor neuropathy, or sensory neuropathy, any of which is of Grade 1 or higher, based on the DAIDS criteria, Version 2.1 (see Appendix 3)
    a. Coadministration of vincristine (maximum: 2 mg/dose) with a dosing interval of every 21 days or less frequent is permitted in subjects without a history of ataxia, persistent tremors, intracranial haemorrhage, motor neuropathy, or sensory neuropathy ***AND*** not receiving concomitant azole therapy during the course of the study (from signing the informed consent to the follow-up visit on Day 30 ± 5).
9. Subject status is unstable (e.g., with sepsis or disseminated intravascular coagulation) and unlikely to complete required study procedures
10. Subject is currently receiving an echinocandin (or has received an echinocandin within 5 days before administration of rezafungin)
11. Previous participation in this study or any previous rezafungin study
12. Participation in another interventional treatment trial with an unapproved investigational agent or presence of an unapproved investigational device at the time of informed consent or within 28 days preceding study entry (informed consent)

    ***Note***: Participation in investigational trials involving approved chemotherapeutic or immunological regimens, investigational radiotherapy trials, and observational trials are allowed.
13. Pregnant or lactating females
14. The Investigator is of the opinion the subject should not participate in the study
15. Subjects/LARs dependent on the Sponsor, Investigator or study site

16. Unable to give his/her own informed consent if a subject reaches the age of consent during the study
17. Committed to an institution in accordance with an order issued either by the judicial or the administrative authorities
18. Tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by a nucleic acid amplification test or antigen test within 7 days prior to dosing of rezafungin (note, SARS-CoV-2 testing is not a protocol requirement and should be performed according to the institutional policy and clinical need)

### 6.3 Lifestyle Considerations

It is expected that all the subjects will receive rezafungin IV infusion in a hospital setting; subjects may be permitted to complete PK assessments on an outpatient basis if deemed appropriate by the Investigator.

### 6.4 Screen Failures

After signing the informed consent, subjects who drop out or withdraw from the study for any reason without completing all Screening evaluations, or subjects who do not meet the eligibility criteria will be considered screen failures.

Subjects who do not meet the criteria for participation may be rescreened. Subjects are only allowed to be rescreened once; the entire screening process must be repeated. Rescreened subjects will be assigned a new subject number for every screening/rescreening event.

# 7 STUDY TREATMENT

The details of the study treatment (IV rezafungin) are provided in Table 3.

## 7.1 Study Treatment Administered

This is an open-label study and all subjects will receive a single IV infusion of rezafungin over 2 hours (± 5 minutes).

***Part 1 (Group 1 – 12 to <18 years of age)***

The IP formulation used for Group 1 will be same as the one used in the adult clinical trials. Dose for Group 1 will be 3 mg/kg (not to exceed a total dose of 200 mg).

***Part 2 (Group 2 – 6 to <12 years and Group 3 – 2 to <6 years of age) and Part 3 (Group 4 – from birth to <2 years of age)***

In parallel to this clinical study, a formulation development programme is being undertaken to identify a lower strength paediatric specific formulation with an appropriate PS80 level for use in subjects <12 years of age. When an adequate paediatric formulation is identified, after the completion of Group 1, the study will be paused and a substantial amendment will be submitted to enable the paediatric formulation to be used in the subjects in Groups 2, 3, and 4.

The planned dose for Group 2 and Group 3 is 4 mg/kg (not to exceed a total dose of 200 mg) and the planned dose for Group 4 is 5 mg/kg; however, the doses will be confirmed after assessment of the interim PK and safety data. The doses may be adjusted as appropriate.

**Table 3 Study Treatment Administered**

| Study Treatment | Test Product |
|---|---|
| **Study Treatment Name** | Rezafungin acetate (MR907) |
| **Treatment Description** | Part 1: Rezafungin is a sterile product of lyophilised powder for reconstitution with sterile water for injection prior to dilution into infusion bags containing normal saline, half-normal saline, or 5% dextrose.<br>Each single-dose vial contains rezafungin acetate (200 mg of active rezafungin) and excipients, including polysorbate 80 (450 mg), mannitol (500 mg), and histidine (47 mg).<br>The formulation may contain hydrochloric acid and/or sodium hydroxide as needed for pH adjustment.<br>After reconstitution of the lyophilised powder with water for injection, the reconstituted solution should be immediately diluted into infusion bags containing normal saline, half-normal saline or 5% dextrose.<br>Part 2 and Part 3: Formulation information will be included when available. |
| **Formulation** | Powder for concentration for solution for infusion (for Part 1).<br>Formulation for Part 2 and Part 3 will be included when available. |
| **Unit Dose Strength** | 200 mg/vial (for Part 1) |
| **Dose(s)** | Age-appropriate doses (as a single dose)<br>• 3 mg/kg (not to exceed a total dose of 200 mg) for 12 to <18 years (Group 1)<br>• 4 mg/kg (not to exceed a total dose of 200 mg) for 2 to <12 years (Group 2 and Group 3)<br>• 5 mg/kg for subjects from birth to <2 years (Group 4) |
| **Route of Administration** | Intravenous infusion over 2 hours (± 5 minutes) |
| **Packaging and Labelling** | Labelling and packaging of study medication will be as per applicable regulatory requirements.<br>Study medication must be stored in a secure, limited access area, and may be dispensed only by specifically authorised personnel.<br>Refer to the Pharmacy Manual for further details on packaging, labelling, and storage. |
| **Manufacturer** | Patheon, Monza, Italy |

## 7.2 Administration

Subjects will receive a single IV dose of rezafungin as a 2-hour (± 5 minutes) IV infusion.

For Group 1, rezafungin will be reconstituted with water for injection. The reconstituted solution should be immediately diluted into infusion bags containing normal saline, half-normal saline or 5% dextrose. Age-appropriate volumes (based on body weight) will be used to dilute reconstituted rezafungin with final concentrations between 0.8 and 1.6 mg/mL. Infusion rates will differ based on the volume of each dose in each subject, and will between 0.9375 and 1.875 mL/kg/hour. The PS80 infusion rate will be 0.0563 mg/kg/min. Please refer to the

Pharmacy Manual for the detailed directions for preparation and administration of rezafungin intravenous solution.

Once the paediatric formulation for Groups 2, 3, and 4 is available, the method of administration will be determined and included in the protocol via a substantial amendment.

### 7.3 Preparation/Handling/Storage/Accountability

The study treatment will be supplied to the Investigator or designee by the Sponsor, either directly or via a local warehouse contracted by the Sponsor.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received, and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment, and only authorised site staff may supply or administer study treatment. All study treatment must be stored in the packaging to protect from light, in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Unused study treatments including empty containers, are to be returned to the Sponsor or Sponsor-designated warehouse at the conclusion of the study, unless provision is made by the Sponsor for destruction of supplies and containers at the investigational site.

Further guidance and information for the final disposition of unused study treatments are provided in the Pharmacy Manual.

### 7.4 Measures to Minimise Bias: Randomisation and Blinding

Not applicable as this is an open-label, single-arm study.

### 7.5 Treatment Compliance

The IP (rezafungin) will be administered at the site (hospital). Subjects will receive the infusion from the Investigator or designee, under medical supervision. The date and time of the infusion and dose administered will be recorded in the source documents. The dose of IP and subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

Compliance will be documented in the source documents and relevant medical and pharmacy records. Deviation(s) from the prescribed dose regimen (e.g., dose, infusion volume, and infusion duration) should be recorded.

## 7.6 Dose Modification

If any mild local infusion-related reaction occurs, the Investigator may temporarily slow or discontinue the infusion, or re-site the infusion. If any systemic or moderate/severe local infusion-related reaction occurs, the Investigator may stop the infusion and inform the Sponsor/medical monitor.

### 7.6.1 Treatment Overdose

For this study, any dose of rezafungin greater than the stipulated dose will be considered an overdose.

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities until resolution, stabilisation of the event, the event is otherwise explained, or the subject is lost to follow-up.
- Obtain an additional blood sample for PK analysis if requested by the medical monitor (to be determined on a case-to-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

## 7.7 Concomitant Therapy

Any medication taken by the subject or administered to the subject other than the IP specified in the protocol (including medication administered for treatment of AEs) is considered concomitant medication. Information about concomitant medications will be recorded in the eCRF from the Screening visit until Follow-up (Day 30 ± 5 days).

Administration of any other antifungal medication classified as an azole or polyene (as standard-of-care), will be allowed.

Using a concomitant echinocandin as the standard-of-care, or having received an echinocandin within 5 days before planned dosing with rezafungin, is not permitted in the study. However, if following dosing with rezafungin, a subject requires the administration of another echinocandin due to medical needs judged by the Investigator, it will be allowed after at least 7 full days after dosing with rezafungin.

Medications that are ongoing at study entry (after the informed consent) and any medication given to the subjects during the study (after the informed consent) through the last study evaluation (Follow-up [Day 30 ± 5 days]) must be recorded on the source documents and appropriate section of the eCRF. The use of any concomitant medication must relate to an AE or the subject's medical history. The medication must be recorded with:

Reason for use

Dates of administration including start and end dates

Dosage information including dose, frequency, and route of administration

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

### 7.7.1 Rescue Medication

For the purpose of this study, there is no specific rescue medication.

# 8 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/ WITHDRAWAL

## 8.1 Discontinuation of Study Treatment

This is a single-dose study. All subjects enrolled will receive a single infusion of IP (rezafungin).

**Stopping Rules**

***Stopping Criteria for an Individual Subject***

- In case of any systemic reaction (i.e., cytokine release syndrome, including nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath) or local infusion-related reaction (i.e., injection site pain or tenderness, erythema or redness, induration or swelling, or pruritis) with a severity of Grade 2 or higher (according to the DAIDS criteria, Version 2.1), the infusion will be immediately stopped and not restarted, and treatment provided as appropriate. The date and time of discontinuation must be recorded in the eCRF. The Sponsor/medical monitor must be informed immediately (no later than 24 hours of Principal Investigator's knowledge of the event). Where feasible, the PK assessment will continue if the subject is well enough and willing to continue. ***Note:*** in case of Grade 1 local reactions, the investigator may slow down the infusion or temporarily discontinue the infusion (see Section 7.6).
- A subject becomes pregnant.

***Criteria for Pausing or Stopping the Study***

The study would be paused in cases where:

- One subject experiences a serious unexpected adverse event that is considered at least possibly related to rezafungin. The event will be investigated and the causality established before dosing the next available subject.

The study would be stopped in cases where any of the following occurs:

- A study drug-related significant adverse reaction (i.e., a serious AE considered at least possibly related to the IP administration) leading to treatment discontinuation in 2 subjects
- Two or more subjects have experienced a Grade ≥4 AE considered to be related to rezafungin
- The Investigator and the Sponsor both agree that the tolerability profile is unacceptable, based on the frequency and intensity of observed AEs (including serious and related AEs)
- At the request of the DSMB, based on a safety concern during the review of the safety and tolerability data

- Additional data from other clinical trials or toxicological studies become available that negatively influence the risk/benefit assessment
- At a specific site/in a specific region: if the local regulatory authority or Independent Ethics Committee (IEC) withdraws approval of the study

### 8.2 Subject Discontinuation/Withdrawal from the Study

Participation in the study is strictly voluntary.

- A subject has the right to withdraw from the study at any time for any reason.
- The subject's parent(s)/LAR (as applicable) may choose to withdraw the subject from the study at any time or the subject may be withdrawn at any time at the discretion of the Investigator for safety (due to AEs or SAEs), or compliance reasons.
- At the time of discontinuation from the study, if possible, an ET visit should be conducted, as shown in the SoA. For data to be collected at the time of study discontinuation see SoA (Table 1 and Table 2). The subject will be permanently discontinued from the study treatment and the study at that time.
- If the subject or subject's parent(s)/LAR 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 or the subject's parent(s)/LAR may request destruction of any samples taken and not tested, and the Investigator must document this in the source documents and relevant medical records. Samples not yet tested at the time of destruction request will be destroyed.
- The reason for withdrawal will be recorded in the eCRF.

### 8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for the scheduled Follow-up visit 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 or the subject's parent(s)/LAR and ascertain whether 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 or the subject's parent(s)/LAR (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 medical record.

- Should the subject or the subject's parent(s)/LAR continue to be unreachable, he/she will be considered to have withdrawn from the study.

# 9 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timings are summarised in Table 1 and Table 2.

Any safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all subjects screened and to confirm eligibility or record reasons for screen failure, as applicable.

Investigations conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for Screening or baseline purposes provided the investigations meet the protocol-specified criteria and were performed within Day -3 to Day -1.

Blood samples for plasma PK determination (rezafungin plasma levels) will be collected in all subjects.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The blood volume for PK and other laboratory tests will not exceed the volume limits recommended by the EU paediatric guidance[21] (up to approximately 3% of total weight [2.4 mL blood/kg body weight], with no more than 1% [0.8 mL blood/kg body weight] at any single time).

For subjects <2 years of age (Group 4), a maximum total of 1 mL of blood will be taken for PK sampling.

## 9.1 Efficacy and/or Immunogenicity Assessments

Not applicable.

## 9.2 Safety Assessments

Safety will be assessed through incidence of TEAEs, including infusion-related and local infusion-site reactions, electrocardiograms (ECGs), clinical laboratory evaluations (including haematology, blood chemistry and urinalysis), vital signs, and physical examination findings.

Any clinically significant observations, as determined by the Investigator, in results of clinical laboratory, 12-lead ECGs, vital signs, or physical examinations will be recorded as AEs.

Planned timepoints for all safety assessments are provided in the SoA (see Table 1 and Table 2).

### 9.2.1 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and serious AEs (SAEs) can be found in Appendix 3.

The subject/subject's parent(s)/LAR, or a caregiver will be asked in general terms about any AEs at regular intervals during the study. In addition, all AEs reported spontaneously by the subject/subject's parent(s)/LAR, or a caregiver during the course of the study will be recorded.

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 until resolution, all AEs that are serious, considered related to the study treatment or that caused the subject to discontinue the study treatment.

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.

### 9.2.2 Time Period and Frequency for Collecting AE and SAE Information

All AEs/SAEs will be collected from the start of IV infusion until the Follow-up visit at the timepoints specified in the SoA (see Table 1 and Table 2).

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours from the time of awareness, 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 information on 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 treatment or study participation, the Investigator must promptly notify the Sponsor.

### 9.2.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow up each subject. All SAEs and AEs of special interest (as defined in Section 9.2.6) will be followed up until resolution, stabilisation, the event is otherwise explained, or the subject is lost to follow-up. Further information on follow-up procedures is provided in Appendix 3.

### 9.2.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment 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 a study treatment under clinical investigation. The

Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IECs, and Investigators.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the study documents and will notify the IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

All confirmed (laboratory-tested positive result) and suspected cases of COVID-19 that occur from the signing of informed consent through the Follow-up visit, whether symptomatic or not, will be reported as AEs.

### 9.2.5 Pregnancy

Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of study treatment and until the time period for reporting pregnancies (should align with the time period for post-treatment contraception determined in Section 6.1).

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female subject or female partner of a male subject (after obtaining the necessary signed informed consent from the female partner) pregnancy. All pregnancies will be followed up for the outcome of pregnancy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

### 9.2.6 Adverse Event of Special Interest

In addition to SAEs, the following are considered an adverse event of special interest (AESI) and should be promptly reported to the Sponsor within 24 hours of awareness through the Reporting of SAEs process as defined in Appendix 3, even if the nature of the AE is deemed non-serious according to the usual regulatory criteria.

***Infusion-related reactions***

Events that, in the opinion of the Investigator, may represent intolerance of the IV infusion of the IP. In general, these events would be temporally associated with the IV infusion of the Sponsor's IP.

***Phototoxicity***

Due to results from a nonclinical phototoxicity study in rats and a Phase 1 clinical trial indicating that rezafungin causes an increased risk for phototoxicity, classified as mild, subjects should be advised to avoid sun and other UV light exposure without adequate protection from Day 1 to Day 8 (i.e., including 7 days after the administration of rezafungin). Investigators should report any AE potentially related to or suspicion of phototoxicity to the Sponsor.

***Neurological manifestations (such as ataxia, tremor and neuropathy)***

In a rezafungin 3-month toxicity study in monkeys, there were observations of tremors, and histology with Schwann cell hypertrophy/hyperplasia (reversible) and phospholipidosis in the dorsal root ganglia first appearing at Week 6 of dosing and at 9.2-fold the exposure to the dosing regimen of rezafungin used in the Phase 3 pivotal study. Ataxia, axonal neuropathy, hypoesthesia, hyperesthesia, paraesthesia, peripheral neuropathy (motor, sensory, or sensorimotor), polyneuropathy, toxic neuropathy, and tremors will be considered AESIs.

### 9.2.7 Physical Examination

A complete physical examination is to be performed at Screening and Follow-up. At all other time points, a brief targeted examination is to be performed as clinically indicated, driven by the subject's symptoms and signs. A complete and brief targeted physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and central and peripheral neurological systems.

### 9.2.8 Vital Signs

Vital signs will be measured in a sitting or supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

### 9.2.9 Electrocardiograms

Single 12-lead ECG(s) will be obtained as outlined in the SoA (see Table 1 and Table 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECGs will be judged by the Investigator for clinical significance.

### 9.2.10 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and see Table 1 and Table 2 for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the aetiology should be identified, and the Sponsor notified.
- All protocol-required laboratory tests, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA (Table 1 and Table 2).
- If laboratory values from non-protocol-specified laboratory tests performed require a change in subject management or are considered clinically significant by the Investigator then the results must be recorded.

## 9.3 Pharmacokinetic Assessment

### 9.3.1 Collection of Blood Samples for Pharmacokinetic Assessment

At the time points defined in the SoA (Table 1), blood samples of 1 mL each will be collected for the analysis of rezafungin plasma concentration. For subjects from birth to <2 years of age (Group 4; Table 2), a maximum total of 1 mL of blood will be taken for PK sampling. The blood samples will be taken via an indwelling IV catheter or arterial line or by direct venepuncture. The exact times of blood sampling will be recorded in the eCRF.

The method of PK blood draws is at the discretion of the Investigator (e.g., via indwelling central venous catheter, port-a-cath, arterial line, or peripheral phlebotomies). However, it is advised to avoid taking PK samples from the same catheter used for rezafungin administration, especially for the end-of-infusion timepoint. In subjects with an indwelling central venous catheter or port-a-cath, it is recommended to administer rezafungin via an alternative line (e.g., a peripheral line) and obtain all PK samples via the central venous catheter or port-a-cath. For procedures for taking PK samples from an indwelling catheter, follow the site's standard of care to prevent contamination of PK samples from the dose administered.

Samples collected for analyses of rezafungin plasma concentration may also be used to evaluate safety aspects related to concerns arising during the study.

Details on sample collection, handling, storage, and shipping will be described in the Laboratory Manual.

### 9.3.2 Pharmacokinetic Assessments for Part 1 and Part 2

Subjects enrolled in Part 1 (aged 12 to <18 years) and Part 2 (aged 2 to <12 years) will undergo PK sampling as described below:

Blood samples will be collected for measurement of plasma rezafungin concentrations at the following 5 timepoints: at end-of-infusion ± 15 minutes, then between 3 and 4 hours after start of infusion, between 6 and 8 hours after start of infusion, at 48 hours (± 4 hours) after start of infusion, and at 168 hours (± 12 hours) after start of infusion. The exact time and date of the PK samples must be recorded.

Approximately 5 mL of blood (5 samples, 1 mL each) will be taken from each subject for the measurement of rezafungin concentrations.

#### 9.3.3 Pharmacokinetic Assessments for Part 3

In Part 3, blood samples for measurement of plasma rezafungin concentrations will be collected at the following 3 timepoints: at end-of-infusion ± 15 minutes, at 24 hours (± 4 hours) after start of infusion, and at 168 hours (± 12 hours) after start of infusion. The exact date and time of the PK samples must be recorded.

A maximum total of 1 mL of blood (3 samples) will be taken from each of the 8 subjects for the measurement of rezafungin concentrations.

### 9.4 Genetics *OR* Pharmacogenomics

Genetics are not evaluated in this study.

### 9.5 Biomarkers

Biomarkers are not evaluated in this study.

### 9.6 Immunogenicity Assessment

Not applicable.

### 9.7 Health Economics OR Medical Resource Utilisation and Health Economics

Health economics OR medical resource utilisation and health economics parameters are not evaluated in this study.

# 10 STATISTICAL CONSIDERATIONS

The Statistical Analysis Plan will be finalised prior to database lock. It will include a more technical and detailed description of the statistical analyses described in this section.

## 10.1 Sample Size Determination

No formal sample size calculation was performed. It is estimated that at least 8 subjects per age range will enable estimation of rezafungin PK in subjects from birth to <18 years of age.

## 10.2 Statistical Hypotheses

No statistical hypotheses are planned for the study.

## 10.3 Analysis Sets

The following populations will be used

**Table 4 Definition of Analysis Populations**

| Populations Analysis Set | Description |
|---|---|
| **Enrolled set** | All subjects who sign the ICF |
| **Safety analysis set** | All subjects who receive any amount of the rezafungin infusion |
| **PK analysis set** | All subjects who receive the single IV infusion of rezafungin and provide at least one blood sample for measurement of rezafungin plasma concentration |
| ICF=Informed Consent Form; IV=intravenous; PK=pharmacokinetic | |

## 10.4 Statistical Analyses

### 10.4.1 General Considerations

In general, continuous data will be summarised by group using descriptive statistics. Categorical data will be summarised by group as the number and percentage of subjects in each category.

Baseline is defined as the last value prior to IV infusion of rezafungin (Screening).

### 10.4.2 Demographic and Baseline Characteristics

Demographics (including age [chronological age], sex, and race) and baseline characteristics (including height, weight, and disease characteristics) will be presented descriptively, overall and by group.

### 10.4.3 Primary Endpoints Analyses

For Parts 1 and 2, PK parameters are primary endpoints for this study. The following PK parameters will be determined: $C_{max}$, $T_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, CL, $V_{ss}$, $V_z$, and $t_{1/2}$.

For Part 3, as only three plasma concentrations will be determined from each subject, there will not be sufficient data to determine PK parameters. Therefore, the plasma concentrations will be listed and summarised using descriptive statistics.

For details see Section 10.5.

### 10.4.4 Secondary Endpoints Analyses

Safety will be assessed through treatment-emergent AEs (TEAEs), SAEs, AESIs, clinical laboratory tests, vital signs, 12-lead ECGs, and physical examination.

The Safety Analysis Set will be used for the analysis of safety data.

### 10.4.5 Adverse Events

Adverse events will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) coding system to give a SOC and Preferred Term (PT) for each AE.

A treatment-emergent AE (TEAE) is defined as any event not present prior to the administration of the IP infusion or any event already present that worsens in either severity or frequency following exposure to the IP.

Only treatment-emergent AEs will be summarised.

The number and percentage of subjects experiencing TEAEs will be summarised by group, severity, and relation to IP. TEAEs will be summarised by MedDRA SOC and PT. All AEs will be listed by subject. The number and percentage of subjects reporting at least one TEAE will be summarised by PT nested within SOC for each group (Groups 1, 2, 3, and 4), and overall, for each of the following AE types:

- Any TEAE
- Any related TEAE
- Any severe TEAE
- Any related severe TEAE
- Any SAE
- Any related SAE
- Any SAE leading to death
- Any AE leading to discontinuation
- Any AE requiring additional therapy

The number and percentage of subjects with any AE will be summarised by the DAIDS grades as follows:

- Mild (Grade 1): Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated
- Moderate (Grade 2): Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
- Severe (Grade 3): Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated
- Life-threatening (Grade 4): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death
- Death (Grade 5): all deaths related to an AE

### 10.4.6 Laboratory Values

All laboratory data will be converted to International System of Units for reporting and processing purposes.

Clinical laboratory data to be summarised include haematology, blood chemistry, and urinalysis. The clinical laboratory parameters to be assessed are listed in Appendix 2.

Clinical laboratory parameters at each timepoint and change from baseline to each post-baseline timepoint will be summarised using descriptive summary statistics for each parameter by group. Clinical laboratory values for each parameter will be assigned an LNH classification according to whether the value is lower (L), within (N) or higher (H) than the reference range for that parameter. The values will be summarised using shift tables from baseline to worst on study result with respect to reference range values (low, normal, high) for each parameter by group. Clinical significance of the laboratory value change will be stated.

### 10.4.7 Vital Signs, Electrocardiogram, and Physical Examination

Vital signs and ECG parameters will be listed and presented descriptively, where applicable.

Vital signs include temperature, pulse rate, respiratory rate, and blood pressure (systolic blood pressure and diastolic blood pressure). Vital sign parameters at each timepoint, and change from baseline to worst on study result will be summarised using descriptive summary statistics for each parameter by group. The normal ranges of vital signs are listed in Appendix 5.

The 12-lead ECG data will be summarised by group and listed by patient. ECGs will be judged by the Investigator as clinically significant (yes/no). The number and percentage of subjects with clinically significant ECG findings will be summarised by group for each timepoint. Any abnormal findings in the continuous ECG monitoring will listed.

Abnormal physical examination findings will be described and listed by group and scheduled timepoint.

## 10.5 Pharmacokinetic Measurements and Analyses

### 10.5.1 Drug Concentration Measurements and Analysis

Individual and mean plasma concentrations at each sampling timepoint for rezafungin will be presented by listings and descriptive statistics including: n, mean, standard deviation (SD), standard error (SE), geometric mean, coefficient of variation expressed as percent (CV%), median, minimum and maximum, as well as quartiles (Q1 and Q3).

### 10.5.2 Pharmacokinetic Parameters

For Parts 1 and 2, the following PK parameters will be determined from the rezafungin concentration-time data using non-compartmental methods (Phoenix WinNonlin®, Build 8.0.0.3176 or higher, Certara USA, Inc., Princeton, New Jersey, US) and actual sampling times:

| | |
|---|---|
| $C_{max}$ | Maximum observed plasma concentration |
| $t_{max}$ | Time at which the maximum plasma concentration was observed |
| $AUC_{0-t}$ | Area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration |
| $AUC_{0-\infty}$ | Area under the plasma concentration-time curve from time 0 extrapolated to infinity |
| $t_{1/2}$ | Terminal elimination half-life |
| $\lambda z$ | Terminal elimination rate constant |
| CL | Total clearance |
| $V_{ss}$ | Volume of distribution at steady-state |
| $V_z$ | Apparent volume of distribution during the terminal phase |

### 10.5.3 Pharmacokinetic Evaluation

Summary statistics of PK parameters including means, geometric means, medians, ranges, SDs, and CVs around the arithmetic and geometric means will be presented by group.

All PK parameters will be calculated by non-compartmental analysis.

## 10.6 Interim Analysis

No formal interim analysis is planned for this study.

A DSMB has been appointed for this study. Three interim reviews by the DSMB are planned during this study: one after completion of Part 1, the second review after 50% of data from Groups 2 and 3 (Part 2) are available, and a third interim review after completion of Part 2. For

the third DSMB review, PK and safety data from both Part 1 and Part 2 will be included for review.

Part 1: The first interim review will be performed after completion of Group 1. Review of safety and PK data by the DSMB will be performed after all subjects in Group 1 have completed the Follow-up visit. Recruitment for Group 2 and Group 3 will be started only after DSMB completes the review and confirms the safety. The dose and PK sampling timepoints for Part 2 may be adjusted as appropriate after assessment of the PK and safety data of Part 1.

Part 2: After the review of data from Group 1 by the DSMB and a decision to proceed to Part 2, enrolment in Group 2 and Group 3 will be started in parallel. A second interim review by DSMB is planned when data from 50% of the subjects enrolled in Part 2 are available. The second interim review of the safety and PK data will be performed to ensure that the exposure achieved in subjects from this age group is safe and well tolerated, and inform whether adjustments to the dose and PK sampling timepoints are required for the remaining subjects. Recruitment/dosing in Group 2 and Group 3 will not be paused during DSMB review 2.

Part 3: A third DSMB review will be performed when Part 2 is completed. Enrolment for Group 4 will not start until the juvenile animal toxicity studies are completed, the animal safety data have been reviewed, and the safety and tolerability from the preceding Parts have been confirmed by the DSMB. The dose and sampling time points may be adjusted as appropriate after assessment of the PK and safety data of Part 1 and Part 2.

### 10.7 Population PK Modelling

The PK data from all groups may also be analysed using nonlinear mixed-effects modelling. Any PK modelling will be subject to a separate analysis plan and will be reported separately from the clinical study report for this study.

# 11 APPENDICES FOR SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

### Regulatory and Ethical Considerations

This study will be conducted in accordance with the CSP and in accordance with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) international ethical guidelines.
- Applicable ICH GCP guidelines.
- Applicable local laws and regulations.

The CSP, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) will be submitted to an IEC by the Investigator for review and approval prior to the eligibility screening.

Any amendments to the CSP will require IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

CSPs and any substantial amendments to the CSP will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.

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 Code of Federal Regulations Title 21 (21 CFR), ICH guidelines, the IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

### 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.

### Informed Consent Process

Informed consent and assent should be obtained by means of a Subject/Patient Information Sheet and ICF, prepared in accordance with ICH E6 and applicable local regulations, written in

non-technical, age-appropriate language. The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the subject *or* their LAR (an individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial) and answer all questions regarding the study.

- Subjects must be informed that their participation is voluntary. Subjects or their parent(s)/LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (Protection of Human Subjects), local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study 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.
- A copy of the ICF(s) must be provided to the subject or their LAR.

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

**Data Protection**

In this trial processing of personal data will be carried out on behalf of the Sponsor by the CRO/the data processor, governed by a contract and strictly according and subject to the General Data Protection Regulation (GDPR) and any applicable data protection rules and regulations. As such, the Sponsor will treat data according to personal data Regulation (EU) 2016/679, and any other applicable national and international regulation. The Sponsor and the CRO/data processor will implement appropriate technical and organisational measures to ensure a level of security appropriate to the risk, taking into account the state of the art, the costs of implementation and the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons. Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The Sponsor will ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the CRO.

- All information generated in this trial is considered highly confidential and must not be disclosed to any person or entity not directly involved with the trial unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IEC personnel, the Sponsor and its authorised representatives are allowed full access to the records. All personal details will be treated as confidential by the Investigator and staff at the CRO. Prior to the processing, the Sponsor will perform an assessment of the impact of the envisaged processing operations on the protection of personal data (according to Article 35 of the GDPR). In the event of a data breach being identified, the Sponsor commits to notifying the relevant data protection supervisory authority and the individuals affected.

- Subjects and/or his/her LAR 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. All personal identifiers according to applicable regulations (e.g., name, phone number) must be redacted permanently by the site personnel and replaced with the subject's unique identification number in all records and data before transfer to the Sponsor (or designee).
- The subject and/or his/her LAR 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 and/or his/her LAR who will be required to give consent for their data to be used as described in the informed consent.
- The subject and/or his/her LAR 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.

**Committees Structure**

**Data Safety Monitoring Board**
Subject safety will be monitored by the DSMB during the study. Details for composition of the DSMB will be included in the DSMB charter.

All safety data collected will be summarised and reviewed by the DSMB for agreement of next steps.

In particular, data will be reviewed by the Sponsor for identification of the events that would potentially contribute to a requirement to pause/stop the study.

Enrolment will be paused during the first and third DSMB reviews. If a pausing/stopping rule is met, a decision will be made, based on the review, as to whether enrolment in the study will be allowed to resume.

**Data Quality Assurance**
All subject data relating to the study will be recorded on eCRFs 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 eCRF.

Guidance on completion of eCRFs will be provided in the CRF completion guidelines.

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, including definition of study critical data items and processes (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., CROs).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 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.

**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 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.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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 CSP and any other study agreements, ICH GCP, and all applicable regulatory requirements.

**Publication Policy**

- The Sponsor will determine the identity of the Co-ordinating Investigator for the study who will review and sign off the clinical study report. This decision will be based on involvement in the study including, but not limited to, study design, subject recruitment and interpretation of study data.
- Clinical studies will be registered in public databases and summary results released / disseminated via publicly available clinical study databases according to the Sponsor's standard operating procedures and local requirements. As a general rule, both Phase 1 Healthy Volunteer studies and studies using a medicinal product in the normal course of medical practice (for example Non-Interventional Studies and Post Marketing Surveillance studies), are excluded from the above public registration and reporting requirements. If such studies do require public registration and/or reporting, this will be undertaken according to local requirements.
- The Sponsor registers clinical studies and posts the summary results as follows:
    - For clinical studies carried out exclusively within the European Union, through the EU Clinical Trial Register (EudraCT) www.clinicaltrialsregister.eu;

- Following the end of the clinical study, the summary results should be made publicly available according to accepted timelines and requirements, usually within 12 months of study completion. Special note should be taken to ensure timelines for the release of paediatric study results are met, which may be 6 months from study completion.
- For multi-site studies, it is mandatory that the first publication be based on data obtained from all analysed subjects; therefore, Investigators participating in multi-site studies must not present data gathered individually or by a subgroup of sites prior to the full, initial publication, unless this has been agreed to by all other Investigators and the Sponsor. Publication of clinical study results may include the presentation of such work at national and international congresses, symposia, professional meetings, peer-reviewed journals, and via other appropriate channels. Named authors and contributors to such publications shall be determined by the Sponsor in accordance with both the Company Publication Policy (which can be found at: http://www.mundipharma-rd.eu/research-areas/publications.html) and the generally accepted criteria for authorship as outlined by the International Committee of Medical Journal Editors authorship guidelines. The data associated with any publication will be and shall remain the sole property of the Sponsor; the copyright of the document may be transferred to the scientific peer-reviewed journal prior to and as part of the publication process, as appropriate.
- Subject to the paragraph above, the site may publish or present the results of the clinical study subject to the protection of the Sponsor or its nominee(s) intellectual property rights, know-how, and its proprietary information. The Sponsor must be furnished with a copy of any proposed publication or presentation at least 60 days prior to submission for review and comment. Upon notice by the Sponsor, however, that the Sponsor intends to secure its intellectual property rights (for example, file a patent application relating to the study) or that Sponsor requires for its know-how or proprietary information to be removed prior to such publication, such publication may be delayed for a further 6 months or until its intellectual property rights have been secured, whichever is the later. The site further agrees that Sponsor’s reasonable comments in relation to the proposed publication will be incorporated into the publication.

## Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 5 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 6 of the CSP. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

**Table 5 Safety Laboratory Tests**

| Laboratory Tests | Parameters |
|---|---|
| Haematology | Complete blood count (platelet count, RBC, haemoglobin, haematocrit, RBC indices: MCV, MCH, % reticulocytes, WBC with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils) |
| Clinical chemistry | Alkaline phosphatase (ALP), BUN, ALT/SGPT, AST/SGOT, total and conjugated bilirubin, creatinine, total protein and albumin, glucose (fasting or non-fasting), potassium, sodium, calcium |
| Routine urinalysis | Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick<br>Microscopic examination (if blood or protein is abnormal) |
| Pregnancy testing | Urine pregnancy test (for postmenarchal females) |
| Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; MCH: Mean corpuscular haemoglobin; MCV: Mean corpuscular volume; RBC: Red blood cell count; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; WBC: White blood cell. | |

## Appendix 3: AEs and SAEs: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

### Definition of AE

| AE Definition |
|---|
| • An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment.<br>• NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment. |
| **Definition of Unsolicited and Solicited AE** |
| • An unsolicited AEs is an AE that was not solicited using a subject diary and that is communicated by a subject/subject's parent(s)/legally authorised representative (LAR) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs.<br>• Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, emergency room visit, or visit to/by a healthcare provider). The subject/subject's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of subject/subject's parent(s)/LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the subject's records.<br>• Unsolicited AEs that are not medically attended nor perceived as a concern by the subject/subject's parent(s)/LAR(s) will be collected during an interview with the subject/subject's parent(s)/LAR(s) and by review of available medical records at the next visit.<br>• Solicited AEs are predefined local at the injection site and systemic events for which the subject is specifically questioned. |
| **Events Meeting the AE Definition** |
| • Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (i.e., not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected treatment-intervention interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment 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 NOT Meeting the AE Definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition<br>• 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<br>• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)<br>• 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 |
| **Adverse Events of Special Interest** |
| • In addition to SAEs, the following AESIs should be promptly reported to the Sponsor within 24 hours of awareness through the SAE reporting process even if the nature of the AE is deemed non-serious according to the usual regulatory criteria<br>• The AESIs for this study are infusion-related reactions, phototoxicity, adverse events suggestive of neurotoxicity (e.g., ataxia, neuropathy, and tremors) |

## Definition of SAE

| **An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br>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**<br>• In general, hospitalisation signifies that the subject has been admitted (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 fulfils 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.<br>• Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. |
| **d. Results in persistent or significant disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) that 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**<br>• Medical or scientific judgement should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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.<br>o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse. |

## 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.<br>• The Investigator will then record all relevant AE/SAE information.<br>• For all AEs, the Investigator must obtain adequate information about the event, severity, time of occurrence (including whether the AE onset was before, during, or after the IP administration if the AE started on the dosing day), duration, and any action, e.g., treatment/follow-up tests. The outcome of the event should be provided along with the Investigator's assessment of the relationship to the IP. The Investigator must also assess whether the event meets the criteria for classification as an SAE.<br>• 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 terms serious and severe are not synonymous. The general term "severe" is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is usually associated with events that pose a threat to a patient's life or ability to function.<br><br>Investigators will grade all AEs by severity using DAIDS (Version 2.1). If an AE is not listed in the DAIDS criteria, a corresponding grading is to be performed by the Investigator based on his/her best medical judgement as follows:<br><br>• Mild (Grade 1): Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated<br>• Moderate (Grade 2): Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated<br>• Severe (Grade 3): Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated<br>• Life-threatening (Grade 4): Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death<br>• Death (Grade 5): all deaths related to an AE |

**Assessment of Causality**

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The Investigator will use clinical judgement to determine the relationship.
- 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.
- 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 an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- **Causality:**

  **Related**

  - Related: The AE follows a reasonable temporal sequence to IP administration, and it is a known reaction to the drug under study or a related chemical group or is predicted by known pharmacology
  - Possibly related: There is a clinically plausible time sequence between onset of the AE and study treatment administration, but the AE could also have been caused by the concurrent/underlying illness, other drugs, or procedures. Information regarding study treatment withdrawal may be lacking or unclear. “Possible” should be used when study treatment administration is one of several biologically plausible causes of the AE.
  - Unlikely related: The AE is most likely due to a non-study-treatment-related cause. However, association with the study treatment cannot be completely ruled out.

  **Not related**

  - Unrelated: Another cause of the AE is most plausible, and a clinically plausible temporal sequence is inconsistent with the onset of the AE and study treatment administration and/or a causal relationship is considered biologically implausible.

**Follow-up of AEs and SAEs**

- During the study (and after the follow-up visit), all AEs and SAEs should be followed proactively by the Investigator until the event resolves or the condition stabilises to a level acceptable to the Investigator, until the event is otherwise explained, or until the subject is lost to follow-up. At the time the subject’s study participation ends, all ongoing AEs and SAEs should be evaluated for resolution.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

## Reporting of SAEs

**SAE Reporting to ICON safety team via Paper Data Collection Tool**

- The primary mechanism for reporting an SAE to ICON safety team will be the paper data collection tool.
- Email of the SAE paper data collection tool is the preferred method to transmit this information to ICON safety team.
- In rare circumstances and in the absence of email, notification by fax of a copy of the SAE data collection tool is acceptable.
- For safety reports received via fax, the receipt date and time (initial or follow-up) are recorded electronically by the ICON PVS fax system and are sent from ICON's fax server system to ICON's mhgsafety@iconplc.com email inbox. Then this will be distributed to ICON safety team for processing.
- Contacts for SAE reporting can be found below.

| | |
|---|---|
| Drug Safety and PV | Email: MHGSafety@iconplc.com<br>Fax: +44 1792 525 720 |

## Appendix 4: List of Prohibited Concomitant Neurotoxic Medications

| LIST OF PROHIBITED NEUROTOXIC CONCOMITANT MEDICATIONS [a] | |
|---|---|
| **Definite High Risk** | |
| vinca alkaloids (Vincristine) with a dosing interval more frequent than every 21 days | |
| taxols (paclitaxel, docetaxel, cabazitaxel) | |
| **Moderate Risk** | |
| amiodarone (Cordarone) | leflunomide (Arava) |
| arsenic trioxide (Trisenox) | lenalidomide (Revlimid) |
| bortezomib (Velcade) | metronidazole/misonidazole (extended use) |
| brentuximab vedotin (Adcetris) | nitrofurantoin (Macrodantin, Furadantin, Macrobid) |
| cetuximab (Erbitux) | nitrous oxide |
| cisplatin & oxaliplatin | nivolumab (Opdivo) |
| colchicine (extended use) | pembrolizumab (Keytruda) |
| dapsone [b] | perhexiline (not used in the United States) |
| didanosine (ddI, Videx) | pomalidomide (Pomalyst) |
| dichloroacetate | stavudine (d4T, Zerit) |
| disulfiram (Antabuse) | suramin |
| eribulin (Halaven) | thalidomide |
| gold salts | vinca alkaloids (Vincristine) with a dosing interval of every 21 days or less frequent [c] |
| ipilimumab (Yervoy) | |
| ixabepilone (Ixempra) | zalcitabine (ddC, Hivid) |

a. Adapted from the Charcot Marie Tooth Association list of neurotoxic medications.

b. Dapsone is prohibited as a concomitant medication with rezafungin in this study.

c. Maximum dose of vincristine is 2 mg/dose. Subjects who receive vincristine should not receive concomitant azole therapy during the course of the study (from signing the informed consent to the follow-up visit on Day 30 ± 5).

## Appendix 5: Reference Ranges for Vital Signs

**Normal Vital Signs by Age**

| Age | Heart Rate (beats/min) | Systolic/Diastolic Blood Pressure (mmHg) | Respiratory Rate (breaths/min) |
|---|---|---|---|
| Premature | 120 – 170 | 55–75 / 35–45 | 40 – 70 |
| 0 – 3 months | 110 – 160 | 65–85 / 45–55 | 30 – 60 |
| 3 – 6 months | 100 – 150 | 70–90 / 50–65 | 30 – 45 |
| 6 – 12 months | 90 – 130 | 80–100 / 55–65 | 25 – 40 |
| 1 – 3 years | 80 – 125 | 90–105 / 55–70 | 20 – 30 |
| 3 – 6 years | 70 – 115 | 95–110 / 60–75 | 20 – 25 |
| 6 – 12 years | 60 – 100 | 100–120 / 60–75 | 14 – 22 |
| >12 years | 60 – 100 | 100–120 / 70–80 | 12 – 18 |

Source: The Harriet Lane Handbook (Johns Hopkins Hospital). 22nd Edition.[22]

| Normal Temperature Ranges | |
|---|---|
| **Measurement Method** | **Normal Temperature Range** |
| Rectal | 36.6°C to 38°C (97.9°F to 100.4°F) |
| Ear | 35.8°C to 38°C (96.4°F to 100.4°F) |
| Oral | 35.5°C to 37.5°C (95.9°F to 99.5°F) |
| Axillary | 34.7°C to 37.3°C (94.5°F to 99.1°F) |

Source: Temperature measurement in paediatrics[23]

## Appendix 6: BMI Charts

# GIRLS UK
## Body mass index (BMI)
## 2-20 years

RCPCH Royal College of Paediatrics and Child Health
DH Department of Health

Please place sticker (if available) otherwise write in space provided.

Name:

NHS/CHI No:

Hospital No:

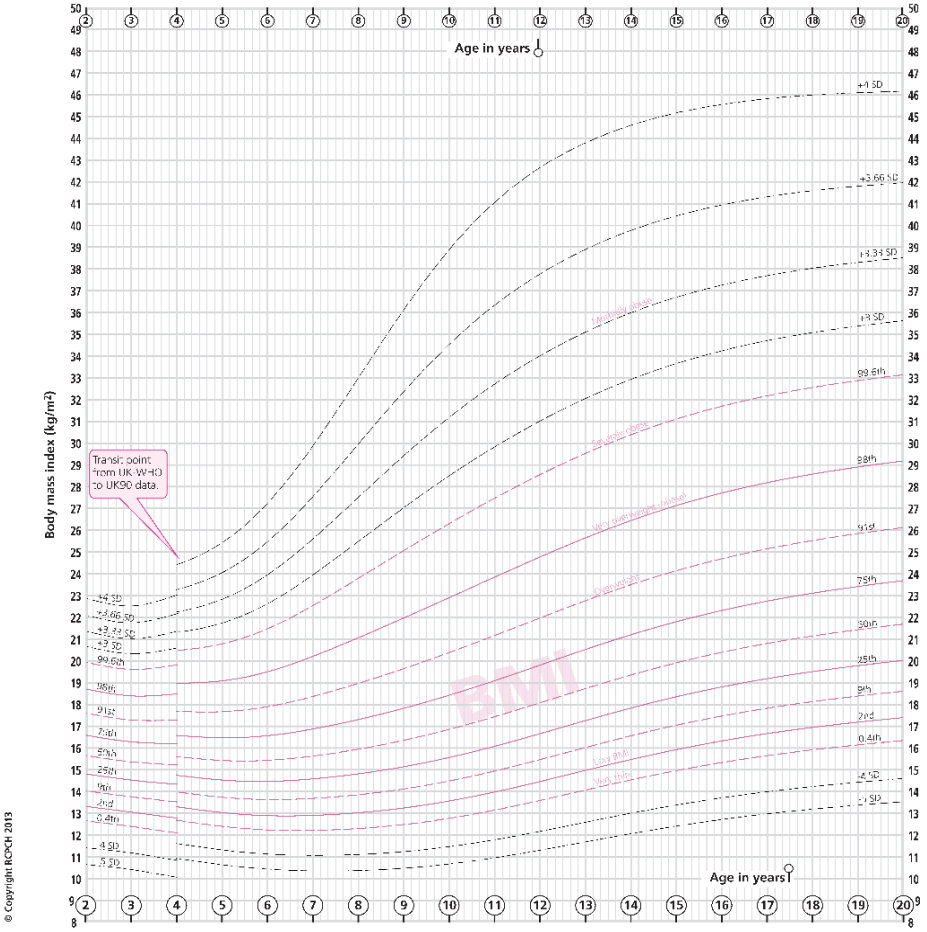
Date of Birth: / /

The BMI centile is a simple and reliable indicator of thinness and fatness in childhood. Where severe over- or underweight is a concern, or where there is a need for monitoring over time, BMI can be calculated and plotted on this chart. It is important also to plot the height and weight separately on the main 2-18 chart. There is also a BMI centile look-up on the standard 2-18 chart for less complex cases.

BMI is calculated by dividing weight (in kg) by the square of height (in metres e.g. 1.32 m, not centimetres e.g. 132 cm).
A simple way to do this on a calculator or mobile phone is:
1. Enter the weight. 2. Divide by height. 3. Divide the result by height.
The result can then be plotted on the chart below.

**Overweight and obesity**
A BMI above the 91st centile suggests overweight. A child above the 98th centile is very overweight (clinically obese) while a BMI above the 99.6th centile is severely obese. In addition to the usual nine centile lines, the BMI chart displays high lines at +3, +3.33, +3.66 and + 4 SD, which can be used to monitor the progress of children in overweight treatment programmes.

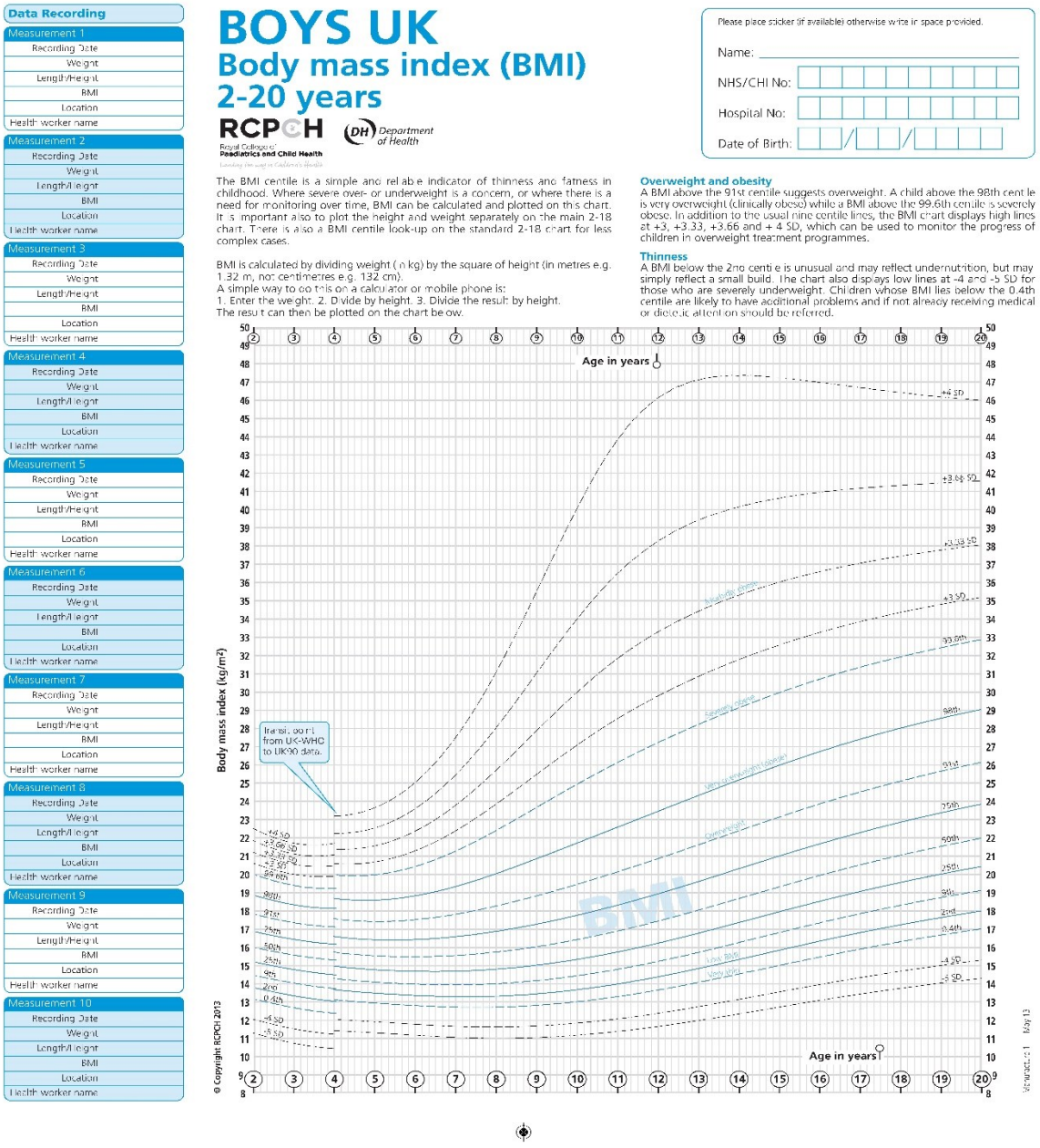
**Thinness**
A BMI below the 2nd centile is unusual and may reflect undernutrition, but may simply reflect a small build. The chart also displays low lines at -4 and -5 SD for those who are severely underweight. Children whose BMI lies below the 0.4th centile are likely to have additional problems and if not already receiving medical or dietetic attention should be referred.






**Data Recording**

| Measurement 1 | Measurement 2 | Measurement 3 | Measurement 4 | Measurement 5 | Measurement 6 | Measurement 7 | Measurement 8 | Measurement 9 | Measurement 10 |
|---|---|---|---|---|---|---|---|---|---|
| Recording Date | Recording Date | Recording Date | Recording Date | Recording Date | Recording Date | Recording Date | Recording Date | Recording Date | Recording Date |
| Weight | Weight | Weight | Weight | Weight | Weight | Weight | Weight | Weight | Weight |
| Length/Height | Length/Height | Length/Height | Length/Height | Length/Height | Length/Height | Length/Height | Length/Height | Length/Height | Length/Height |
| BMI | BMI | BMI | BMI | BMI | BMI | BMI | BMI | BMI | BMI |
| Location | Location | Location | Location | Location | Location | Location | Location | Location | Location |
| Health worker name | Health worker name | Health worker name | Health worker name | Health worker name | Health worker name | Health worker name | Health worker name | Health worker name | Health worker name |




Source: Royal College of Paediatrics and Child Health[24]

## Appendix 7: Paediatric Index of Mortality 2 (PIM2)

| Variable |
|---|
| 1. Systolic blood pressure (SBP), mmHg. If the patient is in cardiac arrest, record SBP=0; if the patient is shocked and the blood pressure is so low that it cannot be measured, record SBP=30; if unknown, record SBP=120. |
| 2. Pupillary reactions to bright light (>3 mm and both fixed=1, other or unknown=0). Do not record an abnormal finding if this is due to drugs, toxins or local eye injury. |
| 3. $PaO_2$, mmHg (unknown=0), and $FiO_2$ at the time of $PaO_2$ if oxygen via ETT or headbox (unknown=0) |
| 4. Base excess in arterial or capillary blood, mmol/L (unknown=0) |
| 5. Mechanical ventilation at any time during the first hour in ICU (no=0, yes=1), including mask or nasal CPAP or BiPAP or negative pressure ventilation |
| 6. Elective admission to ICU (no=0, yes=1), including admission after elective surgery or admission for an elective procedure (e.g., insertion of a central line), or elective monitoring, or review of home ventilation. An ICU admission or an operation is considered elective if it could be postponed for >6 hours without adverse effect. |
| 7. Recovery from surgery or a procedure is the main reason for ICU admission (no=0, yes=1), including a radiology procedure or cardiac catheter. Do not include patients admitted from the operating theatre where recovery from surgery is not the main reason for ICU admission (e.g., a patient with a head injury who is admitted from theatre after insertion of an ICP monitor; in this patient the main reason for ICU admission is the head injury). |
| 8. Admitted following cardiac bypass (no=0, yes=1). These patients must also be coded as recovery from surgery. |
| 9. High-risk diagnosis. Record the number in brackets. If in doubt record 0.<br>[0] None<br>[1] Cardiac arrest preceding ICU admission, including both in-hospital and out-of-hospital arrests, requiring either documented absent pulse or external cardiac compression. Do not include past history of cardiac arrest.<br>[2] Severe combined immune deficiency<br>[3] Leukaemia or lymphoma after first induction<br>[4] Spontaneous cerebral haemorrhage (e.g., from aneurysm or AV malformation). Do not include traumatic cerebral haemorrhage or intracranial haemorrhage that is not intracerebral (e.g., subdural haemorrhage).<br>[5] Cardiomyopathy or myocarditis<br>[6] Hypoplastic left heart syndrome; includes only cases where a Norwood procedure or equivalent is or was required in the neonatal period to sustain life<br>[7] HIV infection<br>[8] Liver failure is the main reason for ICU admission, either acute or chronic, including patients admitted for recovery following liver transplantation for acute or chronic liver failure<br>[9] Neuro-degenerative disorder, requiring a history of progressive loss of milestones or a diagnosis where this will inevitably occur |
| 10. Low risk diagnosis. Record the number in brackets. If in doubt record 0.<br>[0] None |

| Variable |
|---|
| [1] Asthma is the main reason for ICU admission |
| [2] Bronchiolitis is the main reason for ICU admission, including children who present either with respiratory distress or central apnoea where the clinical diagnosis is bronchiolitis |
| [3] Croup is the main reason for ICU admission |
| [4] Obstructive sleep apnoea is the main reason for ICU admission, including patients admitted following adenoidectomy and/or tonsillectomy in whom obstructive sleep apnoea is the main reason for ICU admission (and code as recovery from surgery). |
| [5] Diabetic keto-acidosis is the main reason for ICU admission |

Source: PIM2: a revised version of the Paediatric Index of Mortality[25]

Abbreviation: AV=Arteriovenous; BiPAP=Bilevel positive airway pressure; CPAP=Continuous positive airway pressure; ETT=Endotracheal tube; $FiO_2$=Fraction of inspired oxygen; HIV=Human immunodeficiency virus; ICP=Intracranial pressure; ICU=Intensive care unit; $PaO_2$=Arterial oxygen partial pressure; SBP=Systolic blood pressure

## Appendix 8: Abbreviations

| | |
|---|---|
| ACM | All-cause mortality |
| ADL | Activities of Daily Living |
| AE | Adverse events |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| CIOMS | Council for International Organisations of Medical Sciences |
| CNS | Central nervous system |
| CRO | Contract Research Organisation |
| CSP | Clinical Study Protocol |
| CV | Coefficient of variation |
| DAIDS | Division of Acquired Immunodeficiency Syndrome |
| DSMB | Data Safety Monitoring Board |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EMA | European Medicines Agency |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials Database |
| ET | Early termination |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GDPR | General Data Protection Regulation |
| GLP | Good Laboratory Practice |
| IB | Investigator's Brochure |
| IC | Invasive candidiasis |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IFD | Invasive fungal disease |
| IFI | Invasive fungal infection |
| INR | International normalised ratio |
| IP | Investigational product |
| IV | Intravenous |
| LAR | Legally authorised representative |
| LC-MS/MS | Liquid chromatography-tandem mass spectrometry |
| mITT | Microbiological intent-to-treat |
| NOAEL | No observed adverse effect level |
| PI | Principal Investigator |
| PS80 | Polysorbate 80 |
| PK | Pharmacokinetic(s) |
| PT | Preferred term |
| SAE | Serious adverse event |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SE | Standard error |
| SD | Standard deviation |
| SoA | Schedule of Assessments |

| | |
|---|---|
| SOC | System organ class |
| SOP | Standard Operating Procedures |
| SUSAR | Suspected unexpected serious adverse reactions |
| TEAE | Treatment-emergent adverse event |
| ULN | Upper limit of normal |
| US | United States |
| UV | Ultraviolet |

## Appendix 9: Protocol Amendment History

### Amendment 3 (18 Jul 2023)

Overall Rationale for the Amendment: This amendment is to clarify the neurotoxicity risk of vinca alkaloids (one of the prohibited neurotoxic concomitant medications).

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.2 Exclusion Criteria; Appendix 4: List of Prohibited Concomitant Neurotoxic Medications | Addition of the dosing frequency of vinca alkaloids to define the risk level of neurotoxicity; addition of the maximum dose of vincristine | To clarify the neurotoxicity risk of vinca alkaloids |

### Amendment 2 (26 May 2023)

Overall Rationale for the Amendment: This amendment is to incorporate the updates requested by the European Medicines Agency (EMA) and UK Medicines and Healthcare products Regulatory Agency (MHRA) to have a global protocol and to update the safety reporting processes.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Table 1: Schedule of Assessments for Part 1 and Part 2 | Addition of vital sign assessments to all visits on Day 1; clarification of PK sampling procedure in withdrawn subjects in the footnote | To align with study procedure |
| 6.2 Exclusion Criteria | Clarification of criterion #12 | To clarify the criterion |
| 6.2 Exclusion Criteria and 10.4.5 Adverse Events | Changed adverse event grading from CTCAE to DAIDS | The DAIDS grading system has age-specific definitions |
| 3.3 Benefit and Risk Evaluation, 9.2.6 Adverse Event of Special Interest and Appendix 3 AEs and SAEs: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting | Updated safety reporting process to delete EDC and to change preferred method; specified the duration required for protection from phototoxicity | To align with the study's Safety Management Plan; to clarify the duration for phototoxicity |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Throughout | Editorial changes | Minor editorial changes associated with text added or removed based on the above changes and correcting typographical errors in referencing. |

**Amendment 1 (UK) (17 Apr 2023)**

Overall Rationale for the Amendment: This amendment is based on requests from the Medicines & Healthcare products Regulatory Agency (MHRA).

This amendment is considered to be non-substantial based on the criteria set forth in the medicines for human use (clinical trials) regulation 2004 S.I. 2004/1031.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 6.1 Inclusion Criteria | Removed 'abstinence' from criterion #6 | Based on a request for information from MHRA |

**Amendment 1 (16 Mar 2023)**

Overall Rationale for the Amendment: This amendment is based on requests from the European Medicines Agency (EMA).

This amendment is considered to be 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.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Table 1: Schedule of Assessments for Part 1 and Part 2; and 5.1.5 Follow-up or Early Termination | Addition of a pregnancy test at the follow-up visit. | Based on a request for information from EMA |
| 3.3 Benefit and Risk Evaluation | Addition of confirmation that pivotal nonclinical studies were conducted in accordance with all applicable laws and regulations. | Based on a request for information from EMA |
| 3.3 Benefit and Risk Evaluation | Addition of a description of the methods of analysis of nonclinical pharmacokinetic and toxicokinetic samples. | Based on a request for information from EMA |
| 6.1 Inclusion Criteria | Definition of woman of childbearing potential added to criterion #5. | Based on a request for information from EMA |
| 6.2 Exclusion Criteria | New criterion added: | Based on a request for information from EMA |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | • Subjects/LARs dependent on the Sponsor, Investigator or study site. | |
| 6.2 Exclusion Criteria | New criterion added:<br>• Unable to give his/her own informed consent if a subject reaches the age of consent during the study. | Based on a request for information from EMA |
| 6.2 Exclusion Criteria | New criterion added:<br>• Committed to an institution in accordance with an order issued either by the judicial or the administrative authorities. | Based on a request for information from EMA |
| 6.2 Exclusion Criteria | New criterion added:<br>• Tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by a nucleic acid amplification test or antigen test within 7 days prior to dosing of rezafungin (note, SARS-CoV-2 testing is not a protocol requirement and should be performed according to the institutional policy and clinical need). | Based on a request for information from EMA |
| 8.1 Discontinuation of Study Treatment | Changed individual stopping criteria to be based on the DAIDS severity criteria and not the Investigator's judgement. | Based on a request for information from EMA |
| 8.1 Discontinuation of Study Treatment | New individual stopping criterion added:<br>• A subject becomes pregnant | Based on a request for information from EMA |
| 8.1 Discontinuation of Study Treatment | New study stopping criterion added:<br>• Additional data from other clinical trials or toxicological studies become available that negatively influence the risk/benefit assessment | Based on a request for information from EMA |
| 8.1 Discontinuation of Study Treatment | New study stopping criterion added:<br>• At a specific site/in a specific region: if the local regulatory authority or Independent Ethics | Based on a request for information from EMA |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Committee (IEC) withdraws approval of the study | |
| Appendix 1 Regulatory, Ethical, and Study Oversight Considerations | Addition of description of processes to be followed to protect subjects' data. | Based on a request for information from EMA |
| Throughout | Editorial changes | Minor editorial changes associated with text added or removed based on the above changes and correcting typographical errors in referencing. |

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