# RISK MANAGEMENT PLAN FOR REZAFUNGIN

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**Date for EU-RMP:** 29 September 2023 Version 1.0

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| 5FC | 5-fluorocytosine |
| AE | Adverse event |
| ANC | Absolute neutrophil count |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| AST | Aspartate aminotransferase |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AUC | Area under the concentration-time curve |
| CAD | Cationic amphiphilic drugs |
| CD101 | Investigational product code for rezafungin |
| $C_{max}$ | Maximum concentration |
| CrCl | Creatine clearance |
| CTCAE | Common terminology criteria for adverse events |
| CYP2D6 | Cytochrome P450 2D6 |
| DDI | Drug-drug Interactions |
| ECG | Electrocardiography |
| EEA | European Economic Area |
| EU | European union |
| FDA | Food and Drug Administration |
| GLP | Good laboratory practice |
| IC | Invasive candidiasis |
| ICU | Intensive care unit |
| IFD | Invasive fungal disease |
| IgE | Immunoglobulin E |
| IV | Intravenous |
| LFTs | Liver function test results |
| NOAEL | No observed adverse effect level |
| PIL | Patient Information Leaflet |
| PK | Pharmacokinetic |
| PNS | Peripheral nervous system |
| RMP | Risk management plan |
| SAE | Serious adverse event |
| SmPC | Summary of product characteristics |
| TEAE | Treatment-emergent adverse event |
| QPPV | Qualified person for pharmacovigilance |
| ULN | Upper limit of normal |

| | |
|---|---|
| UV | Ultraviolet |

Note: The terms ‘trial’ and ‘study’ may be used interchangeably throughout.

**European Union (EU)-Risk Management Plan (RMP) for Rezafungin**

**RMP Version to Be Assessed as Part of This Application:**

RMP version number: 1.0

Data lock point for this RMP: 30 August 2023

Date of final sign-off: 29 September 2023

Rationale for submitting an updated RMP: Not Applicable

Summary of significant changes in this RMP: Not Applicable

**Details of the currently approved RMP:** Not Applicable

**Name of EU Qualified Person for Pharmacovigilance (QPPV):**

| | |
|---|---|
| QPPV Name: | **Arthur Meiners** |
| QPPV Declaration: | The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file. |

# PART I PRODUCT OVERVIEW

**Table 1. Product Overview**

| | |
|---|---|
| **Active Substance(s) (INN or common name):** | Rezafungin acetate |
| **Invented name(s) in the European Economic Area (EEA):** | REZZAYO |
| **Marketing Authorisation Holder or Applicant:** | Mundipharma GmbH |
| **Medicinal product to which this RMP refers:** | Rezafungin 200 mg Powder for Concentrate for Solution for Infusion |
| **Marketing authorisation procedure:** | Centralised |
| **Brief description of product:** | |
| **Chemical class:** | Echinocandin class of antifungal drugs |
| **Summary of mode of action** | Rezafungin acts by inhibiting the synthesis of 1,3 ß-D-glucan, an essential component of the fungal cell wall of yeast forms of *Candida* species, regions of active cell growth of *Aspergillus* hyphae, and the early infective stages of *Pneumocystis* (asci/cyst); 1,3- ß -D-glucan is not present in mammalian cells |
| **Important information about its composition** | $N^{5.1}$,6 anhydro[(4R,5R)-4-hydroxy-2-[$3^4$-(pentyloxy)[$1^1$,$2^1$:$2^4$,$3^1$ terphenyl]-$1^4$ carboxamido]-5-[2-(trimethylazaniumyl)ethyl]-L-ornithyl-L-threonyl-trans-4 hydroxy-L-prolyl-(4S)- 4-hydroxy-4-(4 hydroxyphenyl)-L-threonyl-L-threonyl-(3S,4S)- 3-hydroxy-4-methyl-L-proline] acetate |
| **Hyperlink to the Product information** | REZZAYO SmPC, Labelling, and PIL |
| **Indication(s) in the EEA:** | |
| **Current:** | N/A |
| **Proposed:** | Treatment of invasive candidiasis in adults |
| **Dosage in the EEA:** | |
| **Current:** | N/A |
| **Proposed:** | A single 400 mg loading dose on Day 1, followed by 200 mg dose on Day 8 and once weekly thereafter |
| **Pharmaceutical form(s) and strength(s):** | |
| **Current:** | N/A |
| **Proposed:** | Powder for concentrate for solution for infusion; 200 mg rezafungin (as acetate)/ vial |
| **Is/will the product be subject to additional monitoring in the EU?** | Yes |
| PIL: patient information leaflet; SmPC: summary of product characteristic | |

## PART II SAFETY SPECIFICATION

## PART II - MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATIONS

**Indication:**

Treatment of invasive candidiasis in adults

**Prevalence:**

According to conservative estimates, IC affects more than 250,000 people worldwide every year and is the cause of more than 50,000 deaths (*Kullberg et al. 2015*).

**Incidence:**

IC is the most common fungal disease among hospitalised patients in the developed world. Incidence rates of candidemia have been reported to be between 2 and 14 cases per 100,000 persons in population-based studies (*Kullberg et al. 2015*). Southern European countries had a higher incidence rate with 5.29 cases per 100,000 persons than Northern European countries with incidence rate of 3.77 cases per 100,000 persons and Western European countries with incidence rates of 2.5 cases per 100,000 persons (*Koehler et al. 2019*).

Hospital-acquired incidence of IC particularly in the intensive care units (ICU) was reported to be 7.07 episodes per 1,000 ICU admissions (*Bassetti et al. 2019*).

The species distribution has changed over the past decades. Whereas *Candida albicans* had previously been the dominating pathogen, this species today accounts for only half the isolates detected in many surveys. *C. glabrata* has emerged as an important pathogen in northern Europe, whereas *C. parapsilosis* is more prominent in Southern Europe. *C. parapsilosis* is less virulent than *C. albicans,* and *C. glabrata*. This variation is reflected in the low mortality among patients with *C. parapsilosis* candidemia. However, despite its low virulence, *C. parapsilosis* can thrive in certain clinical settings owing to its ability to adhere to medical devices and its propensity to colonise human skin, characteristics that facilitate nosocomial outbreaks (*Kullberg et al. 2015*).

In recent years, concerns have been raised regarding the emerging fungus, *Candida auris*, due to its resistance to antifungals. Between January 2018 and May 2019, 349 cases of *C. auris* were reported in the European Union/European Economic Area (EU/EEA). The majority of cases (97.1%, n=339) were reported from the United Kingdom or Spain; however, during this period *C. auris* was also reported for the first time in Greece, the Netherlands and Poland (*Plachouras et al. 2020).* As a result, C. *auris ha*s been deemed to pose a serious global health threat by the European Centre for Disease Prevention and Control (*ECDC 2018*).

**Demographics of the Population in the Authorised/Proposed Indication:**

The incidence of IC is age-specific, with the maximum rates observed at the extremes of age. Neonates, particularly those with low birth weight, and preterm infants are at particular risk (*Kullberg et al. 2015*).

Susceptibility to candidemia was increased among European patients who had single-nucleotide polymorphisms in the toll-like receptor 1–interferon-γ pathway (*Kullberg et al. 2015*).

**Risk Factors:**

The presence of central vascular catheters, recent surgery (particularly abdominal surgery with anastomotic leakages), and the administration of broad-spectrum antibiotic therapy constitute the major risk factors for IC.

Additional risk factors include critical illness, with particular risk among patients with long-term ICU stay, chronic pulmonary disease, chronic liver disease, respiratory failure, acute necrotising pancreatitis, haematologic malignant disease, solid-organ transplantation, solid-organ tumours, total parenteral nutrition, haemodialysis, glucocorticoid use, or chemotherapy for cancer, and *Candida* colonisation, particularly if multifocal (*Cornely et al. 2020; Kullberg et al. 2015*).

**Main Existing Treatment Options:**

The three main classes of antifungals available for the treatment of IC are the azoles, the echinocandins and the polyenes (typified by amphotericin B). The pyrimidine analogue flucytosine (5-fluorocytosine [5FC]) is occasionally used as well (usually in combination with amphotericin B). Allylamines (e.g., naftifine and terbinafine) are mainly used for dermatophytoses; the orally available terbinafine is limited by its potent inhibition of cytochrome P450 2D6 (CYP2D6) (*Shapiro et al. 2018*), which makes it problematic to use from the point of view of potential drug-drug interactions (DDI).

Echinocandins have a better adverse effect profile than that of amphotericin B (which is hampered by its nephrotoxicity) (*Sabra et al. 1990; Hughes 2021*) and have been associated with better treatment outcomes than azoles. The improved outcomes were most evident among patients infected with *C. albicans* or *C. glabrata.* Hence, (except for *C. parapsilosis*, which may be less susceptible), the echinocandins are often used as first line therapy for IC (*Kullberg et al. 2015*).

However, there are clinical scenarios in which treatment with azoles may be preferred, such as in the treatment of meningitis, endophthalmitis, and urinary tract candidiasis (conditions in which echinocandins are limited by their pharmacokinetics [PK]).

**Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:**

*Candida* species that colonise the gut invade through translocation or through anastomotic leakage after laparotomy and cause either localised, deep-seated infection (e.g., peritonitis), or candidemia. In patients with indwelling intravascular catheters, candidemia that originates from the gut, or the skin leads to colonisation of the catheter and the formation of biofilm. Fungi are subsequently released from the biofilm, causing persistent candidemia.

Once candidemia has developed, whether from a colonised intravascular catheter or by other means, the fungi may disseminate, leading to secondary, metastatic infections in the lung, liver, spleen, kidneys, bone, or eye. These deep-seated infections may remain localised or lead to secondary candidemia (*Kullberg et al. 2015*).

During candidemia, the fungi in the bloodstream may enter the urine, leading to candiduria. Less frequently, deep-seated candidiasis may occur as a result of ascending pyelonephritis and may either remain localised or lead to secondary candidemia.

Over the years, a progressive shift on the severity and mortality of candidemia has been observed towards older and critically ill patients (*Battistolo et al. 2021).* Mortality among

patients with IC is as high as 40%, even when patients receive antifungal therapy (*Kullberg et al. 2015*).

**Important Co-morbidities:**

Immunosuppression/ neutropenia/ leukopenia (including that induced by human immunodeficiency virus/ glucocorticoids), acute necrotising pancreatitis, critical illness (including the need for abdominal surgery with anastomotic leakages), haematologic malignant disease/ solid-organ transplantation/ solid-organ tumours (with the attendant need for chemotherapy/ radiotherapy), and kidney failure requiring haemodialysis are among the common co-morbidities in patients with IC (C*ornely et al. 2020, Kullberg et al. 2015*).

## PART II - MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage are presented below.

**Overview of the Non-Clinical Studies**

A comprehensive non-clinical package to support clinical development of rezafungin has been conducted and included pharmacology, safety pharmacology, PK, toxicology, genotoxicity, reproductive and developmental toxicity, and phototoxicity studies. Rezafungin was evaluated in rats and cynomolgus monkeys in single dose and exploratory intravenous (IV) studies, and in 2-week, 4-week, 13-week and 26-week IV repeat dose toxicity studies.

**Toxicity**

**Reproductive and Developmental Toxicity**

Rezafungin administration at 30 and 45 mg/kg (approximately 4-5 and 6-7 times the clinical exposure, respectively, based on area under the concentration-time curve (AUC) determined in a separate study) was associated with dose-related testicular degeneration primarily characterised by retained/altered spermatids along with degenerative changes in the epididymis considered secondary to the testicular degeneration that were associated with lower sperm concentration and reduced sperm motility, and/or increased incidences of morphologically abnormal sperm compared with controls. Minimal testicular degeneration that was reversible and considered non-adverse was seen in rats at 13-weeks at the high dose of 45 mg/kg (approximately 7 times the clinical exposure) in the general toxicology study. Rezafungin did not affect female rat fertility or male rat reproductive performance following IV administration at doses up to 45 mg/kg (6.3 times the clinical exposure, based on AUC determined in a separate study). This means that the amount of testicular degeneration was not sufficient to have a functional effect i.e., on mating and fertility. Additionally, no testicular effects were seen in monkey studies conducted to date.

Embryo-foetal development studies in pregnant rats demonstrated no reproductive nor developmental toxicity up to doses of 45 mg/kg, the highest dose tested (approximately 5 times the clinical AUC exposure). In pregnant rabbits, lower mean body weight gains were reported at the high dose of 35 mg/kg (3 times the clinical AUC exposure) but no effects on reproductive or developmental toxicity were observed in the Pivotal Study in Pregnant Rabbits NC-106.

In a pre- and post-natal development study in rats up to 45 mg/kg (approximately five times the clinical exposure, based on AUC determined in a separate study) there were no adverse effects on offspring growth, maturation, or measures of neurobehavioral or reproductive

function. Rezafungin was measurable at low concentrations in maternal milk and in the plasma of the offspring of dosed animals. At 1-hour post dose, rezafungin milk-to-plasma ratio in dams was approximately 0.23 on Lactation Day 8-10 and foetal plasma levels were approximately 3% of the maternal plasma levels on Gestation Day 18-20.

Relevance to human usage:

A discussion on testicular degeneration is detailed further in MODULE SVII.

**Phototoxicity**

Rezafungin absorbs in the ultraviolet A/ B (UVA/UVB) range and thus an in vitro phototoxicity assessment was conducted in 3T3 fibroblasts. Rezafungin, like other echinocandins (e.g., anidulafungin), induced a positive response in vitro.

Rezafungin was tested for phototoxicity potential in rats. Multiple doses were administered every 3 days for a total of 7 days, at dose levels of 15, 30, and 45 mg/kg providing an AUC exposure 4.3-fold above those estimated clinically following a 400 mg IV loading dose. These generated a minimal phototoxic response.

Relevance to human usage:

A discussion on phototoxicity is detailed further in MODULE SVII.

**Genotoxicity**

Rezafungin was negative for genotoxicity in the bacterial and mammalian cell in vitro genetic toxicology studies, and in the bone marrow micronucleus study in rats.

Relevance to human usage:

The genotoxicity studies did not provide any evidence of rezafungin causing mutations or inducing structural chromosomal abnormalities, such as breaks and exchanges and is unlikely to be a genotoxic risk to humans.

**Hepatotoxicity**

Exploratory hepatotoxicity studies were conducted to evaluate the metabolic stability and toxicity of rezafungin compared to anidulafungin at comparable exposure levels.

Rezafungin was evaluated in rats and cynomolgus monkeys in single dose and exploratory IV studies, and in 2-week, 4-week, and 13-week, and 26-week IV toxicity studies. Hepatotoxicity was not observed in rats or monkeys during toxicology testing with rezafungin, but hepatotoxicity has been observed with all other approved echinocandins related to reactive metabolites in non-clinical studies.

For generation of reactive intermediates, rezafungin and anidulafungin were incubated in phosphate-buffered saline (pH 7.4) alone and in the presence of L-glutathione for 24 hours (*Ong et al. 2016*). Samples were analysed to obtain full scan parent and product fragment ions. Following incubation with and without L-glutathione, rezafungin showed metabolic stability with no reactive intermediates formed. In contrast, anidulafungin formed a glutathione adduct during incubation and also a reactive intermediate from the ring opening degradation pathway of anidulafungin.

For the exploratory repeat dose range toxicity and hepatotoxicity screen, rezafungin or anidulafungin at approximate equivalent plasma exposures were administered as IV infusions over 14 days to Sprague-Dawley rats. Animals who received rezafungin did not

exhibit effects on body weight, haematology, coagulation, or urinalysis, and there were no early deaths. In contrast, animals that received anidulafungin had statistically significant increases in mean alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin. There were no microscopic changes in the livers of animals who received rezafungin. With anidulafungin administration, minimal to moderate single cell necrosis affecting the hepatocytes was observed at supratherapeutic doses in some of the females that were considered related to administration of anidulafungin.

Relevance to human usage:

A discussion on hepatotoxicity is detailed further in MODULE SVII.

**Safety Pharmacology**

Rezafungin was tested for effects on neurobehavioral functional endpoints in rats. There were no clinical observations or statistically significant changes in neurobehavioral parameters or body temperature that were attributed to rezafungin administered once every 3 days over 1 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.

Rezafungin did not affect the human ether-a-go-go-related gene current up to the maximum concentration able to be tested (1.1 µM), which exceeds the estimated free maximum concentration ($C_{max}$) plasma levels achieved clinically following a single dose of 400 mg rezafungin.

Administration of a 20-minute IV infusion of rezafungin to telemetered male cynomolgus monkeys, did not cause changes in body temperature, blood pressure, electrocardiographic (ECG) and respiratory parameters up to the highest dose test of 10 mg/kg, but there was a minimal and transient decrease in heart rate relative to vehicle control in restrained animals at ≥3 mg/kg that was of uncertain relationship to rezafungin.

Relevance to human usage:

Although there were no significant cardiovascular findings in the nonclinical studies, a definitive QT/QTc clinical study (CD101.IV.1.06) was conducted, which confirmed no QT prolongation at rezafungin doses up to 1400 mg.

**Tremor**

At the start of the 13-week toxicity study in monkeys when the high dose was 60 mg/kg, unexpected tremors occurred during the 6th week of dosing. This led to the lowering of the high dose from 60 mg/kg to 45 mg/kg, but all the females were euthanised due to the severity of their clinical signs. In the 30 mg/kg dose group, tremors began in the 7th week of dosing, though they occurred much less frequently than in the 60/45 mg/kg group. The low-grade tremors at 30 mg/kg did not interfere with the daily function of the animals and demonstrated reversibility during the 4-week recovery period; therefore, they were considered to be not adverse at this dose. The no observed adverse effect level (NOAEL) for the minor tremoring in the Good Laboratory Practice (GLP) 13-week study was 30 mg/kg. This dose level achieved AUC plasma safety margins approximately 9.2-fold over the estimated plasma exposure in humans following a 400 mg IV single dose.

Due to the presence of tremors, a detailed neuropathology assessment was performed including whole body perfusions and evaluations of plastic embedded and/or silver stained sections of peripheral nerves/axons and sensory ganglia. Test article-related Schwann cell inclusions (considered not adverse) were observed by light microscopy in sensory ganglia

(≥3 mg/kg) and in the peripheral nerves (≥30 mg/kg), with Schwann cell hyperplasia seen at the highest doses tested (≥30 mg/kg). Electron microscopy confirmed that the Schwann cell inclusions were phospholipidosis.

Other than tremors, there were no neurobehavioural effects. Furthermore, nerve conductance velocities were not adversely affected by rezafungin treatment in an investigative 13-week study in monkeys, suggesting that the presence of Schwann cell phospholipidosis in the ganglia and peripheral nervous system (PNS) did not adversely affect nerve signal transduction. The results of two 13-week toxicology studies using cynomolgus monkeys showed no apparent relationship of the minor tremoring to the non- adverse Schwann cell changes. Tremors were not observed in the 13-week rat study.

In the completed 26-week toxicity and toxicokinetic study of rezafungin in mature cynomolgus monkeys, the animals received rezafungin once a week at 0, 5, 15, or 30 mg/kg/dose. Tremors occurred in all groups, including controls, without a dose- or time-related trend in the numbers or severity of tremors, and with a generally comparable incidence between control group and rezafungin treated groups. This was considered to indicate that these tremors represent a set of minor background findings for this cohort of monkeys and is not considered related to rezafungin administration. Consistent with the findings from the 13-week study, there were dose-related Schwann cell inclusions/eosinophilic globules present in dorsal spinal nerve root, peripheral nerves, sympathetic nerves and/or trigeminal nerves, and nerves associated with various organ/tissue sections at all dose levels, and rezafungin-related increased cellularity of likely Schwann cells, in peripheral nerves of 30 mg/kg treated animals. However, sensory and motor nerve conduction remained within functional physiological ranges. The NOAEL was set at 30 mg/kg/dose, the maximum tested dose.

It is notable that there were no measurable rezafungin concentrations in plasma samples from the control animals. Therefore, the generalised tremors observed in control monkeys were not caused by contamination of the control formulation.

Charles River Laboratories Montreal ULC conducted a retrospective analysis to determine the prevalence of incidental clinical observations which could be interpreted as neurologically related in control animals. They compiled clinical observations documented in control animals from 306 GLP-compliant toxicology studies which were conducted between 2009 and 2019 at Charles River Laboratories Montreal ULC (*Authier et al., 2021*). Among the clinical signs compiled which could be interpreted as neurologically related, they observed signs such as salivation, tremors, uncoordinated behaviour, myoclonic jerks, muscle twitches, change in muscle tone, muscle atrophy, full muscle contraction, circling, clonic convulsion, tonic convulsion, hunched back, piloerection and hypersensitivity. Tremors were amongst the most frequently observed in control monkeys at Charles River Laboratories Montreal ULC.

After due consideration, tremors were not considered a risk as they were not adverse at the NOAEL of 30 mg/kg in the 13-week study, and in the 26-week study, tremors were identified in both treatment and control groups. The information provided by Charles River Laboratories in *Authier et al., 2021*, indicates that the generalised tremors observed in the monkey studies is likely explained by the housing conditions and handling of the animals.

Relevance to human usage:

A discussion on tremor is detailed further in MODULE SVII.

### Histamine-Mediated Reactions

Dose-related and transient acute histamine mediated effects in rats were associated with mortality at dose levels of 15 to 45 mg/kg. The NOAEL for these $C_{max}$-driven acute effects was 5 mg/kg which generated $C_{max}$ values of 8.04 and 10.4 µg/mL, in males and females respectively, after the first dose. These rat-specific effects due to histamine release are consistent with observations for marketed echinocandins and some other cationic amphiphilic drugs (CADs) and are thus considered to be of minimal consequence to clinical development in humans.

In the 4-week and 13-week pivotal GLP toxicology studies, rezafungin was administered IV via a slow bolus injection over 3–4 minutes to rats or as an IV infusion over 20–40 minutes to cynomolgus monkeys once every 3 days. Acute clinical signs that were transient after the first dose in surviving rats and generally not seen after the third or fourth dose in repeat dose studies, were related to elevations in plasma histamine levels (based on the findings of a separate rat study). A similar response was not seen in cynomolgus monkeys at $C_{max}$ levels that exceeded those where these effects were seen in rats, consistent with the observation for other marketed echinocandins, which demonstrate rats to have an enhanced sensitivity to this histamine-release response compared to monkeys, dogs, and humans.

Relevance to human usage:

Transient infusion-related reactions have been observed in humans exposed to rezafungin, similar to those observed with other echinocandins. They are characterised by flushing, sensation of warmth, nausea, and chest tightness. For details, please see MODULE SVII. It should be noted that after reconstitution, rezafungin will be diluted into an infusion bag containing either normal saline, half normal saline, or 5% dextrose prior to administration to subjects. This dilution was not carried out for the toxicology studies.

### Ongoing Studies

None

### Planned Studies

None

## PART II - MODULE SIII CLINICAL TRIAL EXPOSURE

The clinical development programme for rezafungin includes the following completed studies:

- Two Phase 1 PK and tolerability studies (CD101.IV.1.01 and CD101.IV.1.02), Phase 1 QT (CD101.IV.1.06), Photosensitivity (CD101.IV.1.07), DDI (CD101.IV.1.09), Excretion/Metabolism/PK (CD101.IV.1.12), hepatic impairment (CD101.IV.1.15), and a second DDI study (CD101.IV.1.17)
- A Phase 2 safety and efficacy study for treatment of candidemia and/or invasive candidiasis (CD101.IV.2.03)
- A Phase 3 study for treatment of candidemia and/or invasive candidiasis (CD101.IV.3.05)

Ongoing studies include a Phase 3 study for the prophylaxis of invasive fungal disease (IFD) in adults undergoing allogeneic blood and marrow transplantation (CD101.IV.3.08), a continuation of a Phase 3 study for treatment of candidemia and/or invasive candidiasis in

Chinese patients (CD101.IV.3.05), a Phase 1 study to evaluate the PK, safety and tolerability of a single IV dose of rezafungin in paediatric patients <18 years of age (MR907-1501), and a Phase 2 study to evaluate the efficacy, safety and tolerability of rezafungin combined with co-trimoxazole in HIV-infected adults with *Pneumocystis jirovecii* Pneumonia.

**Table 2. Overview of Completed Clinical Studies**

| Study Number | Study Title | Number of Subjects/ Dose, Subjects/ Regimen |
|---|---|---|
| **Safety and Pharmacokinetics** | | |
| CD101.IV.1.01 | A Phase 1, Randomized, Double-Blind, Single Dose, Dose-Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of CD101 Injection in Healthy Subjects | 32 subjects/ of which 24 were given rezafungin (50 mg, 6; 100 mg, 6; 200 mg, 6; 400 mg, 6); placebo, 8 |
| CD101.IV.1.02 | A Phase 1, Randomised, Double-Blind, Multiple- Dose, Dose-Escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of CD101 Injection in Healthy Subjects | 24 subjects/ of which 18 were given rezafungin (100 mg, 6; 200 mg, 6; 400 mg, 6); placebo, 6<br>100 mg, once weekly; 2 doses<br>200 mg, once weekly; 2 doses<br>400 mg, once weekly; 3 doses |
| CD101.IV.1.09 | Phase 1, Open-Label Drug-Drug Interaction Cocktail Study with Rezafungin for Injection and Drugs Commonly Used as Substrates for Pharmacokinetic Interaction or Other Drugs | 26 subjects/ all were given rezafungin at the following doses:<br>600 mg on Day 1, 400 mg on Day 10, and 400 mg on Day 15 |
| CD101.IV.1.12 | An Open-Label, Single Dose, Phase 1 Study to Evaluate the Excretion, Metabolism, and Pharmacokinetics of [$^{14}$C] Rezafungin in Healthy Adult Subjects | 9 male subjects/ all were given a single dose of 400 mg rezafungin |
| CD101.IV.1.15 | An Open-Label, Single Dose, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Rezafungin in Adult Subjects with Hepatic Impairment Relative to Matched Controls | 32 subjects (16 with moderate and severe hepatic impairment, 16 matched healthy adults)<br>All were given a single dose of 400 mg rezafungin |
| CD101.IV.1.17 | Phase 1, Open-Label Drug-Drug Interaction Study of Rezafungin for Injection when Coadministered with Cyclosporine, Ibrutinib, Mycophenolate Mofetil, or Venetoclax in Healthy Subjects | 34 subjects/ 32 subjects were given rezafungin/ of which 30 subjects received 400 mg on Day 1, 200 mg on Day 8, and 200 mg on Day 15 / 1 subject received 400 mg then 200 mg/ 1 subject received only one dose of 400 mg. |

| Study Number | Study Title | Number of Subjects/ Dose, Subjects/ Regimen |
|---|---|---|
| **Safety and Pharmacodynamics** | | |
| Photosensitivity study | | |
| CD101.IV.1.07 | A Phase 1, Multiple-Dose Study to Determine the Photosensitivity and Safety of CD101 for Injection in Healthy Subjects | 36 subjects/ of which 12 were given rezafungin 400 mg, 4 doses once weekly: 12; placebo: 12; positive control: ciprofloxacin, 2 doses/day for 1 week: 12 |
| Thorough QT/QTc study | | |
| CD101.IV.1.06 | A Phase 1, Randomised, Double-Blind, Comparative, Placebo and Positive Controlled Study to Evaluate the Safety, Pharmacokinetics, and Effects on the Electrocardiogram of CD101 for Injection in Healthy Subjects | 60 subjects/ of which 24 were given rezafungin: 600 mg, 12; 1400 mg, 12; placebo, 12; positive control: moxifloxacin, 24/ single dose |
| **Pivotal Phase 2 (Safety and Efficacy) study** | | |
| CD101.IV.2.03 | A Phase 2, Multicentre, Randomised, Double-blind Study of the Safety, Tolerability, and Efficacy of Intravenous CD101 vs Intravenous Caspofungin Followed by Oral Fluconazole Step-down in the Treatment of Subjects with Candidemia and/or IC (STRIVE study) | Parts A and B:<br>202 subjects/<br>Group 1: rezafungin: 400 mg weekly × 2 to 4 weeks total, rezafungin: 81 dosed;<br><br>Group 2: rezafungin: 400 mg on Day 1, followed by 200 mg once weekly × 2 to 4 weeks total, 53 dosed;<br><br>Caspofungin daily: 68 dosed |
| **Pivotal Phase 3 (Safety and Efficacy) studies** | | |
| CD101.IV.3.05 | A Phase 3, Multicentre, Randomised, Double-blind Study of the Efficacy and Safety of Rezafungin for Injection versus Intravenous Caspofungin Followed by Optional Oral Fluconazole Step-down in the Treatment of Subjects with Candidemia and/or IC (The ReSTORE Study) | 196 subjects of which 98 were administered rezafungin (400 mg on Day 1, followed by 200 mg once weekly);<br><br>Caspofungin: 98 dosed daily |

## Clinical Trial Exposure by Duration of Exposure

**Table 3. Duration of exposure**

| Duration of exposure to IV rezafungin | Subjects in clinical trials |
|---|---|
| <1 month (1-28 days) | 409 |
| 1 to <3 months | 0 |
| 3 to <6 months | 0 |
| ≥6 months | 0 |
| **Total** | **409** |
| **Total exposure** | **184.2 subject-months** |

**Table 4. Age group and gender**

| Age group | Subjects | | |
|---|---|---|---|
| | Males | Females | Total |
| Adults: 18-64 years | 191 | 119 | 310 |
| Elderly: 65-74 years | 42 | 18 | 60 |
| Elderly: 75-84 years | 16 | 13 | 29 |
| Elderly: >85 years | 5 | 5 | 10 |
| **Total** | **254** | **155** | **409** |

**Table 5. Ethnic origin**

| Ethnic origin | Subjects |
|---|---|
| White | 294 |
| Black or African American | 69 |
| Native Hawaiian or Other Pacific Islander | 0 |
| American Indian or Alaska Native | 2 |
| Asian | 29 |
| Other/ not reported | 15 |
| **Total** | **409** |

## Clinical Trial Exposure in Special Populations

**Table 6. Extent of Exposure in Special Populations**

| Population | Subjects exposed |
|---|---|
| Pregnant / lactating women | 0 |
| Children | 0 |

| Population | Subjects exposed |
|---|---|
| Renal impairment (mild, CrCl >60ml/min) | 142 |
| Renal impairment (moderate to severe, CrCl <60 ml/min) | 77 |
| Hepatic impairment | 40 |
| Cardiac impairment | 91 |
| Sub-populations with genetic polymorphisms | unknown |
| Immunocompromised | unknown |
| CrCl: Creatine Clearance. | |

# PART II - MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

## SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

**Table 7. Exclusion Criteria in Pivotal Clinical Studies**

| Exclusion Criterion | Reason for Exclusion | Considered as Missing Information (Y/N) | Rationale (If not included as missing information) |
|---|---|---|---|
| Children and adolescents (Age <18 years) | A separate paediatric study programme is being implemented according to paediatric investigation plan and Paediatric Committee guidance | No | Rezafungin is not indicated for use in children and adolescents (age <18 years). |
| Pregnant or lactating women | The risks to pregnant or lactating women or the unborn foetus are unknown | No | As described in MODULE SII, no developmental toxicity or safety signals related to use in pregnancy or lactation were identified from non-clinical studies.<br>Routine pharmacovigilance activities are sufficient to further evaluate this topic. |
| Alanine aminotransferase or aspartate aminotransferase levels >10-fold the ULN<br><br>Severe hepatic impairment in subjects with a history of chronic cirrhosis (Child-Pugh score >9) | At the time of conduct of Phase 2 and Phase 3 clinical studies, the impact of hepatic impairment had not been studied.<br><br>An Open-Label, Single Dose, Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Rezafungin in Adult Subjects with Hepatic Impairment Relative to Matched Controls has now been completed | No | Rezafungin PK was examined in subjects with moderate (Child-Pugh B, n=8) and severe (Child-Pugh C, n=8) hepatic impairment. Mean rezafungin exposure was reduced by approximately 30% in subjects with moderate and severe hepatic impairment compared to matched subjects with normal hepatic function. Rezafungin PK was similar in subjects with moderate and severe hepatic impairment, and rezafungin exposure did not change with increasing |

| Exclusion Criterion | Reason for Exclusion | Considered as Missing Information (Y/N) | Rationale (If not included as missing information) |
|---|---|---|---|
| | | | degree of hepatic impairment. Hepatic impairment did not have a clinically meaningful effect on rezafungin PK, therefore, dose adjustments in subjects with hepatic impairment are not necessary. There were no specific safety concerns noted in the study |
| Meets CTCAE criteria for ataxia, tremor, motor neuropathy, or sensory neuropathy of Grade 2 or higher.<br>History of severe ataxia, tremor, or neuropathy or a diagnosis of multiple sclerosis or a movement disorder (including Parkinson's Disease or Huntington's Disease).<br>Planned or ongoing therapy at screening with a known neurotoxic medication | Adverse clinical signs (tremors) were observed at high doses in monkeys but the NOAEL for the minor tremoring in the GLP 13-week study was 30 mg/kg. This dose level generates AUC plasma safety margins approximately 9.2-fold over the estimated plasma level in humans following a single 400 mg loading dose | No | A Follow-up 13-week investigative monkey study with a 13-week recovery period at 30 mg/kg, confirmed the presence of a slight-moderate non-adverse tremoring but no adverse change in nerve conduction. No change in myelin-to-axon nerve ratios was found. These findings confirmed lack of neuronal and central nervous system microscopic changes, including no primary axonal degeneration/ axonopathy. Tremoring reversed after 4-weeks of recovery.<br>In a 26-week toxicity and toxicokinetic study in monkeys, the animals received rezafungin once a week at 0, 5, 15, or 30 mg/kg/dose. Tremors occurred in all groups, including controls, without a dose- or time-related trends in the numbers or severity of tremors. No measurable rezafungin concentrations in plasma samples from the control animal and neurological findings were consistent with the 12-week study discussed above. A retrospective analysis by Charles River Laboratories described in *Authier et al., 2021*, indicated that the generalised tremors observed in the monkey studies was likely due to the housing conditions and handling of the animals |

| Exclusion Criterion | Reason for Exclusion | Considered as Missing Information (Y/N) | Rationale (If not included as missing information) |
|---|---|---|---|
| ULN: Upper limit of normal. | | | |

## SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programme

The clinical development programme is unlikely to detect certain types of adverse reactions such as:

- **uncommon** (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) adverse reactions due to the small safety dataset (234 subjects treated with rezafungin in Phase 2 and 3 clinical studies),
- adverse reactions with a **long latency** due to limitations in long-term exposure (maximum treatment exposure was 30 days in Phase 2 and 3 treatment studies) and
- those caused by **prolonged or cumulative exposure** (mean duration of exposure in the Phase 2 study was 13.0 days and 12.4 days in Phase 3 for rezafungin treated subjects).

## SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

**Table 8. Exposure of Special Populations Included or Not in Clinical trial Development Programme**

| Type of Special Population | Exposure | |
|---|---|---|
| **Use in elderly (Age ≥65 years)** | There is treatment experience in subjects 65 years of age and older. In Phase 2 and 3 studies, 39.5% (n=32) of subjects receiving 400/400 mg dosing were greater than 65 years of age and 16.0% (n= 13) were 75 years of age or older and in the pooled 400/200 mg safety population 42.4% (n=64) were 65 years or older and 17.2% (n=26) were 75 years of age or older.<br>A population PK analysis, including data from Phase 1, Phase 2, and Phase 3 studies, showed that age was not a significant covariate of rezafungin PK. There were no significant differences in TEAEs according to age. No dose adjustments are required in elderly subjects aged 65 years or more. | |
| **Use in pregnancy and lactation** | To date there is no experience with rezafungin in pregnant/ lactating women. | |
| **Renal impairment** | Renal impairment (mild, CrCl >60ml/min) | 142 |
| | Renal impairment (moderate to severe, CrCl <60 ml/min) | 77 |
| **Cardiac impairment** | Subjects with cardiac conditions/medical history were not excluded from Phase 2 and 3 studies. In the rezafungin treatment arms, 91 had a history of cardiac disorders while 18 subjects with a medical history of heart failure were included in Phase 2 and 15 subjects in Phase 3 clinical study. | |
| **Immunocompromised subjects** | Many subjects with IC are immunocompromised (see MODULE SI). Immunocompromised subjects were not excluded from the Phase 2 and 3 studies. In the rezafungin treatment arms, 81.5% subjects had an APACHE II score <20 and 92.1% an ANC ≥500/µL while 21.9% subjects had APACHE II score ≥20 or an ANC <500/µL. | |

| Type of Special Population | Exposure |
|---|---|
| **Subjects with genetic polymorphisms** | No information is available on the percentage of subjects in the clinical development programme with genetic polymorphisms in the toll-like receptor 1–interferon-γ pathway, who may have increased susceptibility to candidemia. |
| TEAEs: treatment emergent adverse events; APACHE: Acute Physiology and Chronic Health Evaluation; ANC: absolute neutrophil count. | |

# PART II - MODULE SV POST-AUTHORISATION EXPERIENCE

## SV.1 Post-authorisation Exposure

REZZAYO was approved by the United States Food and Drug Administration to treat candidemia and invasive candidiasis on 22 March 2023. Marketing commenced on 31 July 2023. Post marketing exposure data is not yet available.

### SV.1.1 Method Used to Calculate Exposure

Not applicable.

# PART II - MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

## SVI.1 Potential for Misuse for Illegal Purposes

Rezafungin is a prescription only medication, normally used in the hospital setting and given intravenously which limits access to the product.

There has been no evidence of psychological or physical dependence, or withdrawal or rebound effects in nonclinical or clinical studies. This is consistent with labelling for marketed drugs in the echinocandin class.

Rezafungin has no significant sedative or euphoric effects and can only be administered by slow infusion. There is no conceivable reason or easy method of administration for use for illegal purposes.

The potential for misuse for illegal purposes is considered non-existent.

# PART II - MODULE SVII IDENTIFIED AND POTENTIAL RISKS

## SVII.1 Identification of Safety Concerns in the Initial RMP Submission

### SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

#### Hepatotoxicity

Hepatotoxicity/liver enzyme elevations have been listed in the SmPCs of other members of the echinocandin class.

Potential mechanism:

The cause of serum aminotransferase elevations during echinocandin therapy is unknown. In nonclinical studies of other echinocandins, the highest drug concentrations were found in the liver; hence, a direct toxic effect or production of a toxic intermediate may be the cause of the abnormalities (*National Institute of Diabetes and Digestive and Kidney Diseases 2012*).

In the generation of reactive intermediates, rezafungin showed metabolic stability with no reactive intermediates formed following incubation with and without L-glutathione. In contrast, anidulafungin formed a glutathione adduct during incubation and also a reactive intermediate from the ring opening degradation pathway of anidulafungin.

Evidence sources and strength of the evidence:

Hepatotoxicity is a potential class effect of the echinocandins (*Birch et al. 2017*) and hepatic adverse events (AEs) appear on the labels of anidulafungin, micafungin and caspofungin.

Transient elevations in liver enzymes have occurred in 2% to 15% (*Mullins et al. 2020*) of patients treated with the echinocandins, typically returning to baseline after withdrawal of therapy. Clinically apparent hepatotoxicity has occurred in isolated cases (*Vekeman et al. 2018*); however, a causal relationship to the antifungal agent is often difficult to prove, as these agents are typically used in persons who are critically ill and have other conditions and treatment regimens that are associated with liver injury. The largest experience has been with caspofungin, which may have a higher rate of serum enzyme elevations than with micafungin or anidulafungin and has more frequently been linked to cases of acute, symptomatic liver injury. Nevertheless, the product labels for anidulafungin, caspofungin, and micafungin all mention AEs of serum enzyme elevations, hepatitis and/or acute liver failure (*National Institute of Diabetes and Digestive and Kidney Diseases 2012*).

Characterisation of the risk:

Nonclinical studies with rezafungin showed no evidence of hepatotoxicity. Rezafungin is also highly stable in human liver microsomes and hepatocytes and following incubation in vitro with and without L-glutathione, rezafungin showed excellent metabolic stability with no reactive intermediate metabolites formed. Studies in human liver microsomes and hepatocytes have shown that rezafungin does not undergo extensive oxidative metabolism.

In the clinical absorption, metabolism, and elimination mass balance study CD101.IV.1.12, a single dose of [14C] labelled rezafungin was administered to nine healthy male adults. This showed that rezafungin is metabolised by hydroxylation and dealkylation, although the primary route of elimination is via faeces as unchanged parent drug.

In the clinical hepatic impairment study CD101.IV.1.15, a single dose of rezafungin 400 mg was administered to eight subjects with severe hepatic impairment and eight subjects with moderate hepatic impairment. There was no statistically significant increase in liver function test (LFTs) results in subjects dosed with rezafungin compared to baseline.

In the Phase 2 study CD101.IV.2.03 (STRIVE), 122 subjects received rezafungin. There were no serious adverse events (SAEs) involving the hepatobiliary system with an incidence of ≥2%, and no TEAEs involving the hepatobiliary system were reported with an incidence of ≥5% (*Thompson 2021*). One subject (0.8%) met laboratory criteria for Hy's Law at Day 2: (ALT or AST) >3 ×ULN, ALP <=2.0 ×ULN, and total bilirubin >2 ×ULN. However, the subject had a motorcycle accident 12 days prior to the screening visit which resulted in multiple

injuries, including an open abdominal wound and subsequent complications including rhabdomyolysis and intra-abdominal infection.

In the Phase 3 study CD101.IV.3.05 (ReSTORE), of the 98 subjects dosed with rezafungin, 6 (6%) met laboratory criteria for Hy's Law after initiation of rezafungin. However, all six of these subjects had elevated LFTs at baseline. One subject had a through and through gunshot wound to the liver, 1 subject was in sickle cell crisis, and another subject had a history of ischaemic hepatitis and was in multiorgan failure when he enrolled. Of the remaining 3 subjects, 1 had multiorgan dysfunction syndrome (including cardiac failure and respiratory failure) as well as septic shock at enrolment. Another had a history of congestive hepatopathy, and he died on Day 17 due to acute respiratory distress syndrome, pneumonia, bronchopulmonary aspergillosis, ventricular tachycardia, and septic shock. The remaining subject had Child-Pugh Class A cirrhosis, was critically ill with multiple infections at enrolment and died on Day 4 from uncontrolled sepsis due to catheter-related bloodstream infection.

In summary, seven subjects from the STRIVE and ReSTORE studies met the laboratory criteria for Hy's Law, however, based on the multiple confounding factors, there was not a reasonable possibility to suspect a drug-induced liver injury in any of these subjects.

Also, in the CD101.IV.3.05 (ReSTORE) study, one of the 98 subjects dosed with rezafungin developed Grade 3 transaminitis with hyperbilirubinemia (considered nonserious) and rezafungin was withdrawn. The LFTs normalised after withdrawal of rezafungin. Seven additional subjects (8 altogether, 8%) had 2 grade increases in transaminases after treatment with rezafungin. However, the transaminase increases may not have been due to rezafungin, as there were confounding factors present such as attribution to another drug. There were no events of liver failure attributable to rezafungin in the clinical studies conducted to date.

Overall, the risk of hepatotoxicity with rezafungin appears to be low both in terms of frequency and severity of events, compared to that occurring with some of the other therapeutic options such as voriconazole and micafungin. Hence, this risk is considered to have minimal clinical impact on patients (in relation to the severity of the indication treated). As a comparison, the respective SmPCs list the frequency of abnormal LFTs as "very common" for voriconazole, and "common" for fluconazole, posaconazole, caspofungin, micafungin, and anidulafungin. The SmPCs list the frequency of liver failure as "uncommon" for voriconazole and micafungin, and "rare" for fluconazole and posaconazole. Fatal hepatic failure has been reported with micafungin use.

Risk factors and risk groups:

The likelihood of severe acute liver injury with other echinocandins (anidulafungin, caspofungin, micafungin) appears to be greatest in patients with pre-existing hepatic insufficiency (*National Institute of Diabetes and Digestive and Kidney Diseases 2012; Vekeman et al. 2018*). Other strong predictors of severe hepatotoxicity included: oesophageal varices, sepsis, and chronic kidney disease stage 4 (*Vekeman et al. 2018*).

Risk-benefit impact and preventability:

Section 4.4 of the SmPC includes the following text under the heading "Hepatic Events":

In clinical trials, elevations in liver enzymes have been seen in some patients treated with rezafungin. In some patients with serious underlying medical conditions who were receiving multiple concomitant medications along with rezafungin, clinically significant hepatic

dysfunction has occurred; a causal relationship to rezafungin has not been established. Patients who develop elevations in liver enzymes during rezafungin therapy should be monitored and the risk/benefit of continuing rezafungin therapy should be re-evaluated.

Section 4.8 of the SmPC includes the following terms with frequency “common”:

- Hepatic enzymes increased
- Blood alkaline phosphatase increased
- Alanine aminotransferase increased
- Aspartate aminotransferase increased
- Blood bilirubin increased

Additionally, “changes in blood tests of liver function” are mentioned in the patient information leaflet (PIL) under Section 4 (as a common side effect that may affect up to 1 in 10 people). This will alert patients and healthcare providers to the possibility of LFT abnormalities, allowing detection at an early stage, which could mitigate seriousness. Based on the available non-clinical and clinical data, the benefit: risk ratio remains positive.

**Reversible Testicular Degeneration**

Potential mechanism:

Retained/altered spermatids, and in some cases, Sertoli cell vacuolation, along with degenerative changes in the epididymis, are considered secondary to the testicular degeneration. The effects on spermatid maturation may be a secondary effect on Sertoli cells which is consistent with a reversible effect on late-stage spermatogenesis. However, these effects did not adversely affect mating or fertility in rats.

Evidence sources and strength of the evidence:

In the male fertility study conducted with rezafungin in rats, testicular degeneration was seen in all males at 45 mg/kg and in the majority of animals at 30 mg/kg. The testicular degeneration was reversible. The degeneration was characterised by retained/altered spermatids, and in some cases, Sertoli cell vacuolation, along with degenerative changes in the epididymis, considered secondary to the testicular degeneration. These findings were associated with lower sperm concentration and reduced sperm motility, and/or increased incidences of morphologically abnormal sperm compared with controls. Despite these testicular effects, rezafungin did not affect mating or fertility in male and female rats following IV administration at doses up to 45 mg/kg (approximately 6-7 times the clinical exposure).

The NOAEL for testicular degeneration in the male fertility study with rezafungin was 15 mg/kg whereas the NOAEL for this change in the 13-week rat study with rezafungin was 45 mg/kg; these doses are 2.0-fold (15 mg/kg) and 7-fold (45 mg/kg) over the predicted human AUC plasma steady state exposure following a 400 mg loading dose and 200 mg once weekly.

The risk to humans is considered to be low because only minimal, reversible changes were identified in the rat studies and no testicular effects were seen in the monkey studies in which rezafungin doses equivalent to more than twice the predicted human exposure were used.

Testicular toxicity was also observed in animal studies with micafungin (*Mycamine SmPC*), and thus the effects seen with rezafungin may be a class effect.

Risk factors and risk groups:

There were no specific risk factors identified in non-clinical and clinical studies.

Risk-benefit impact and preventability:

For the reasons stated above, the need for preventive measures in relation to this risk is considered to be low, hence, there is no significant impact on risk-benefit.

**Tremor**

Potential mechanism:

Tremor is listed in the SmPC of other echinocandins; however, the mechanism has not been reported. In clinical studies with rezafungin, two cases of tremor were considered due to electrolyte imbalance secondary to drug treatment.

Evidence sources and strength of the evidence:

Non-clinical studies were carried out in monkeys for up to 13 weeks where definitive findings related to rezafungin included tremors. A Follow-up investigative study in monkeys at 30 mg/kg confirmed minor non-adverse tremoring. The nonclinical safety results generated support the proposed dose regimen as described in the SmPC. Additionally, in a 26-week dosing study in monkeys, tremors were detected in both treatment and control groups. It is considered that the generalised tremors in all the monkey studies were associated with the housing and handling of the animals, which is supported by the high incidence of tremors in control animals in other studies at the Charles River Laboratories Montreal ULC *(Authier et al., 2021*).

A total of four events of tremor were reported in rezafungin across Phase 2 and Phase 3 studies. There were 2 events of tremor that occurred in the Phase 3 study CD101.IV.3.05 (ReSTORE). The event of tremor that occurred in one subject was reviewed by a neurology expert, who concluded that the tremor was likely caused by hypokalaemia, and the hypokalaemia was likely caused by rezafungin treatment. The event of tremor that occurred in the other subject in study CD101.IV.3.05 was not related to rezafungin but directly attributed to tumour lysis syndrome, caused by chemotherapy for lymphoma indirectly through hypocalcaemia.

Two events of tremor occurred in the Phase 2 study CD101.IV.2.03 (STRIVE). In one subject, the event was not related to rezafungin but was attributed to “fluid shifts with the use of diuretics”. In the other subject, the event was not related to rezafungin but was attributed to recent cerebral infarction.

All four adverse events (AEs) were mild in intensity, and were easily treated by correction of serum electrolytes, or resolved without treatment.

No other AEs suggestive of neurotoxicity (e.g., peripheral neuropathy, tremor, or ataxia) considered related to rezafungin have been reported in the clinical studies completed to date. Also see MODULE SIV.

Risk factors and risk groups:

There were no specific risk factors identified in non-clinical and clinical studies.

Risk-benefit impact and preventability:

Tremors occurred in very few subjects and would be expected to have minimal clinical impact on subjects (in relation to the severity of the existing condition for which subjects are being treated with rezafungin). Three of the four cases of tremor detected in clinical studies with rezafungin were attributed to clinical changes due to the underlying condition. One case of tremor was reviewed by a neurology expert who concluded that tremor was indirectly caused by rezafungin due to hypokalaemia, which was likely directly caused by rezafungin treatment. Therefore, tremor is listed in Section 4.8 of the SmPC with frequency “uncommon” and Section 4 of the PIL.

**Infusion-Related Reactions**

Infusion-related reactions have been listed in the SmPCs of other members of the echinocandin class.

Potential mechanism:

The underlying mechanism for infusion-related reactions is not defined but presents clinically as a histamine-like reaction. It is not thought to be immunologically related.

Evidence sources and strength of the evidence:

Infusion-related reactions (facial flushing, swelling, rash, pruritis, and fever) have been reported with all the echinocandins. They usually occur immediately after infusion and respond well to antihistamines. The drug need not be withdrawn but the rate of infusion should be decreased. Overall, the infusion-related events seem to be much fewer than those due to amphotericin B (*Grover 2010*).

Characterisation of the risk:

Infusion-related reactions may arise from rezafungin (the active substance).

Overall, in the clinical development programme, infusion-related reactions occurred commonly (in 1-10% of subjects administered rezafungin).

These included reactions at the injection site, including rash, pruritus, and pain; as well as generalised reactions such as flushing, sensation of warmth, nausea, and chest tightness. Infusion-related reactions were most commonly observed in subjects receiving multiple doses (i.e., second, third, and later doses) - details below.

In the multiple ascending dose Phase 1 study CD101.IV.1.02, 4 subjects (2.6%) in the rezafungin group experienced mild, transient infusion reactions, characterised by flushing, sensation of warmth, nausea, and chest tightness. These infusion reactions were associated primarily with the 400 mg dose. The reactions occurred within minutes of infusion initiation and disappeared in some subjects within minutes without interruption or discontinuation of the study drug infusion. For those that required interruption of the infusion, restarting the infusion at a lower rate once symptoms had resolved was successful, as prescribed by the study protocols. No other pharmacological or procedural interventions were required or instituted for the infusion reactions.

In another Phase 1 study to investigate the photosensitivity of rezafungin (CD101.IV.1.07), an infusion reaction occurred during the fourth dose of a regimen of 400 mg once weekly for 4 weeks. The third dose had been administered only 3 days prior (instead of 7 days) due to a delay in the return of the subject to the clinic. Symptoms of the infusion reaction resolved within a few minutes of infusion interruption without pharmacological interventions. The

infusion was then restarted and completed at half the usual infusion rate with no resulting adverse symptoms or signs.

One event of infusion-related reaction was also observed in the Phase 2 study (CD101.IV.2.03; STRIVE) in a subject administered 400 mg once weekly. The infusion reaction (severe flushing and chest tightness with shortness of breath) occurred during infusion of the fourth dose and resolved within minutes of infusion discontinuation. There was no rechallenge of study drug.

Four subjects in the rezafungin treatment group experienced six events of infusion-related reaction in the Phase 3 study (CD101.IV.3.05; ReSTORE), of which 1 was considered serious (details below).

- One subject had an infusion-related reaction characterised by rash and wheezing on Day 3 (during placebo administration) and the rash recurred on Day 4 during placebo administration.
- One subject had an infusion-related reaction on Day 1. Two minutes into the infusion, the subject complained that he felt like he was going to pass out, felt very hot and had difficulty breathing. He was also noted to have an elevated heart rate.
- One subject had an infusion-related reaction (generalised transient flushing from the infusion site to the rest of his body and abdominal discomfort) on Day 1 within one minute of starting the infusion; the infusion-related reaction (transient sensation of flushing, a sensation of warmth in his hands and head and transient eye floaters) recurred on Day 8 within one minute of starting the infusion.
- One subject had a serious infusion-related reaction manifesting with scarlatiniform erythema of the trunk and face associated with hypotension and bronchospasm. The reaction occurred thirty minutes into the third infusion (on a day when placebo was scheduled to have been administered). The infusion was stopped and the event resolved. The event was considered related to the study drug; however, as per the randomisation schedule, the last dose of rezafungin would have been administered 2 days prior. The subject received a blood transfusion prior to the Day 3 dose, which was given as a possible alternate causality.

Risk factors and risk groups

Risk factor:

A faster than recommended rate of infusion.

Risk groups:

Subjects with a history of infusion-related reaction to an echinocandin or previous reaction to polysorbate may be at higher risk of this AE.

Preventability:

Subjects with a history of infusion-related reactions can have their next infusion at a slower rate. Rezafungin should be administered by slow IV infusion over approximately 1 hour and may be increased up to 180 minutes and beyond.

Risk-benefit impact:

This risk can be properly managed with controlled infusion rates. Subjects are normally administered rezafungin in a controlled environment using diluted formulations where severe

reactions are unlikely to occur, and where rapid intervention should limit the impact if severe reactions should occur. Risk minimisation activities are detailed in the product information, including SmPC Sections 4.4, and 4.8, and PIL, Sections 2 and 4.

Risk mitigation measures include the option to slow the infusion rate (e.g., infusing the dose in 3 hours rather than 1 hour) to alleviate symptoms.

Since the number of reported subjects with infusion-related reaction is low (1 subject in Phase 2 and 4 subjects in Phase 3), and since the majority were mild and the risk can be adequately managed, the impact on risk-benefit is low.

**Phototoxicity**

Phototoxicity has been listed in the SmPCs of other members of the echinocandin class.

Potential mechanism:

As with other echinocandins, rezafungin absorbs light in the UV (UVA/UVB) range. Absorption of UV-photons by drug molecules can result in structural changes, photolysis, and generation of reactive oxygen species, which can cause dermal toxicity (*Price et al. 2021*).

Evidence sources and strength of the evidence:

Rezafungin was tested for phototoxicity potential in rats. Multiple doses were administered every 3 days for a total of 7 days, at dose levels of 15, 30, and 45 mg/kg. These generated a minimal phototoxic response.

Isolated cases of phototoxicity reactions have been reported in subjects treated with other echinocandins e.g., micafungin (*Price et al. 2021*).

The risk of phototoxicity from rezafungin and other echinocandins appears to be much less than that of voriconazole (*Lewis 2011*), which is thought to be due to its metabolite voriconazole-N-oxide (*Mourad et al. 2018*), and which can lead to aggressive squamous cell carcinoma of the skin and melanoma.

Characterisation of the risk:

An assessor-blinded Phase I study (CD101.IV.1.07) was conducted in healthy subjects. In the rezafungin group, a 400 mg once weekly regimen on days 1, 8, 15, and 22 was administered which provides almost double the exposure compared to the Phase 3 and proposed marketed dose regimen of 400 mg during the first week followed by 200 mg once weekly thereafter. Mild phototoxicity reactions were seen in both the rezafungin group and the positive control (ciprofloxacin) group.

There has been only 1 reported nonserious event of phototoxicity in the other clinical studies conducted with rezafungin to date. A mild event of sunburn has been reported in the Phase 2 Study CD101.IV.2.03 (STRIVE). following prolonged exposure to the sun.

There have been no reported serious events of phototoxicity in the clinical studies with rezafungin.

Risk factors and risk groups:

Patients with Fitzpatrick Skin Type I always burn and never tan. Patients with Fitzpatrick Skin Type II burn easily and tan minimally. Such patients have less photoprotection from melanin compared to patients with the other Fitzpatrick Skin Types, and since skin pigmentation is the main protective factor against the harmful effects of UV radiation (*Kowalska et al. 2021*),

patients with Fitzpatrick Skin Types I and II may be at greater risk for phototoxicity reactions. However, patients with heavily pigmented skin can also develop phototoxicity reactions.

Patients in countries that are closer to equatorial regions might be at higher risk.

Preventability:

All patients, but patients with Fitzpatrick Skin Types I and II especially, should avoid exposure to sunlight or UV radiation without adequate protection during dosing with rezafungin and for up to five half-lives thereafter.

Risk-benefit impact:

Wording has been included in the SmPC Section 4.4 and 4.8, that rezafungin may cause increased risk of phototoxicity, and patients should avoid exposure to sunlight or other sources of UV radiation without adequate protection during treatment and for 7 days after the last administration of rezafungin. Sections 2 and 4 of the PIL also indicates possible higher sensitivity to UV light.

As only 1 mild reaction was seen in patients during the Phase 2 and 3 clinical studies, the impact of phototoxicity on the overall risk-benefit balance of rezafungin is likely to be minimal.

**Hypersensitivity to Rezafungin and Anaphylaxis/Anaphylactic Shock**

Potential mechanism:

Immune hypersensitivity reactions to drugs are mediated predominantly by Immunoglobulin E (IgE) antibodies or T cells (*Schnyder et al. 2009*).

Evidence sources and strength of the evidence:

Allergic reactions to echinocandins have been documented in literature but there are only few reports of anaphylaxis. Life-threatening allergic reactions that might include difficulty breathing with wheezing or worsening of an existing rash have been rarely reported with anidulafungin (may affect up to 1 in 100 people). Anaphylaxis is an identified risk with anidulafungin, caspofungin, and micafungin.

Characterisation of the risk:

Mild- moderate allergic reactions were reported uncommonly, occurring in 0.1-1% of subjects administered rezafungin.

There have been no reported serious events of allergic reactions related to rezafungin use in the clinical development programme to date.

While infusion-related reactions, dose-related and transient, have been seen with rezafungin in both non-clinical and clinical studies (see above section on infusion-related reactions), true immunologically mediated anaphylaxis or anaphylactic shock reactions to rezafungin have so far not been observed in clinical studies. However, due to limited numbers of subjects exposed, possibility of such reactions cannot be excluded.

Risk factors and risk groups:

Cross-reactivity with other echinocandins can occur (*Patel et al. 2009*). Hence, patients with known or suspected allergy to another echinocandin may be at risk of an allergic reaction to rezafungin.

Patients with known or suspected allergies to polysorbate 80 or any of the excipients.

Preventability:

As stated in the SmPC Section 4.3, rezafungin is contraindicated in patients with known hypersensitivity to the other echinocandins and patients with known allergies to any of the excipients. This is also outlined in Section 2 of the PIL.

Risk-benefit impact:

As rezafungin is administered in a controlled environment, any patient with a severe acute reaction during infusion which did not respond to temporary discontinuation or decreased infusion rate, would rapidly be treated as potential anaphylactic reaction. Thus, the impact on the risk-benefit profile is likely limited.

**Off-label Use**

The proposed product label for rezafungin is specific for the treatment of IC in adults only. However, since rezafungin has demonstrated antifungal activity and prophylactic efficacy against other strains of fungal infections such as *Aspergillus* spp., *Pneumocystis* spp. and dermatophytes in pre-clinical studies (*Miesel et al. 2021*, *Hoenigl et al. 2021*), it is possible that rezafungin might be used off–label, prophylactically, in the treatment of other fungal infections, or in paediatric patients.

There are currently no data on use in younger children, which is clearly stated in the (proposed) product label. While the echinocandins are, in many countries, considered first line therapy for IC in children (*Cornely et al. 2012*), since there are other drugs in this class that have been approved for paediatric use, based on the specialist treatment area and proposed labelling, off-label administration of rezafungin to young children is considered unlikely.

Routine pharmacovigilance, including monitoring of the literature will be performed to identify case reports of off-label use.

Risk-benefit impact and preventability:

In light of the above considerations, off-label use is currently only a potential (theoretical) risk; thus, the risk-benefit impact of off-label use is likely to be low.

### SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

None

## SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable as this is the first RMP.

### SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

### SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

None

### SVII.3.2 Presentation of the Missing Information

None

## PART II - MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

**Table 9. Summary of Safety Concerns**

| **Safety Concerns** | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

## PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

### III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

**Specific adverse reaction follow-up questionnaires:**

None

**Other forms of routine pharmacovigilance activities for:**

None

### III.2 Additional Pharmacovigilance Activities

None

## III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable

## PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

No post-authorisation efficacy studies are ongoing or planned for rezafungin.

## PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

### V.1 Routine Risk Minimisation Measures

**Table 10. Description of Routine Risk Minimisation Measures by Safety Concern**

| Safety Concern | Routine Risk Minimisation Measures |
|---|---|
| **Important identified risks** | None |
| **Important potential risks** | None |
| **Important missing information** | None |

### V.2 Additional Risk Minimisation Measure

No additional risk minimisation activities are required.

**Removal of Additional Risk Minimisation Activities**

Not applicable, as this is the first RMP.

## V.3 Summary of Risk Minimisation Measures

**Table 11. Summary of Risk Minimisation Activities**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Important identified risks:** None | | |
| **Important potential risks:** None | | |
| **Important missing information:** None | | |

## PART VI SUMMARY OF THE RMP

**Summary of RMP for REZZAYO (Rezafungin)**

This is a summary of the RMP for REZZAYO . The RMP details important risks of REZZAYO, and how more information will be obtained about REZZAYO's risks and uncertainties (missing information).

REZZAYO's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how REZZAYO should be used.

This summary of the RMP for REZZAYO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of REZZAYO's RMP.

### I. The Medicine and What it is Used For

REZZAYO is indicated for invasive candidiasis in adults and it is given by intravenous route only.

Further information about the evaluation of REZZAYO's benefits can be found in REZZAYO's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

### II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of REZZAYO, together with measures to minimise such risks and the proposed studies for learning about REZZAYO's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks;

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

## II.A List of Important Risks and Missing Information

Important risks of REZZAYO are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of REZZAYO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

**Table II.A.1. List of Important Risks and Missing Information**

| List of Important Risks and Missing Information | |
|---|---|
| **Important Identified Risks** | • None |
| **Important Potential Risks** | • None |
| **Missing Information** | • None |

## II.B Summary of Important Risks

Not applicable.

## II.C Post-Authorisation Development Plan

### IIC.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of REZZAYO.

### IIC.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for REZZAYO.

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# PART VII ANNEXES

## Annex 4: Specific Adverse Event Follow-Up Forms

Not applicable

## Annex 6: Details of Proposed Additional Risk Minimisation Measures

Not applicable.