12 October 2023
EMA/487522/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rezzayo

International non-proprietary name: rezafungin

Procedure No. EMEA/H/C/005900/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Rezzayo
Applicant:	Mundipharma GmbH De-Saint-Exupery-Straße 10 Flughafen 60549 Frankfurt Am Main GERMANY
Active substance:	rezafungin acetate
International Non-proprietary Name/Common Name:	rezafungin
Pharmaco-therapeutic group (ATC Code):	antimycotics for systemic use, other antimycotics for systemic use (J02AX08)
Therapeutic indication(s):	Rezzayo is indicated for the treatment of invasive candidiasis in adults. Consideration should be given to official guidance on the appropriate use of antifungal agents.
Pharmaceutical form(s):	Powder for concentrate for solution for infusion
Strength(s):	200 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

API - Active pharmaceutical ingredient = AS – Active substance

AS – Active substance = API - Active pharmaceutical ingredient

BSE - Bovine spongiform encephalopathy

CMA - Critical material attributes

CoA - Certificate of Analysis

CPP – Critical process parameters

CQA – Critical quality attributes

DS - Drug substance = AS = API

DSC - Differential scanning calorimetry

DSM - Drug product manufacturer

DP - Drug product

DPM - Drug product manufacturer

DoE - Design of experiments

DVS - Dynamic vapor sorption analysis

FIR - Fourier-transform infrared

FP – finished product

GC – gas chromatography

GMP - Good manufacturing practice

HDPE - High density polyethylene

HPLC - High-performance liquid chromatography

ICH – International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

IPC – In-process control

IV - Intra venous

LOD - Limit of detection

LOQ - Limit of quantitation

LoQ – List of questions

LDPE - Low density polyethylene

LOD - Loss on drying

MDD – Maximum daily dose

MO – Major objection

MS – Mass spectrometry

NLT - Not less than

NMT - Not more than

OC – Other concern

Ph. Eur. – European Pharmacopoeia

PBS - Phosphate buffered saline

PDE - Permitted daily exposure

Ph Eur – European Pharmacopoeia

PSD - Particle size distribution

PS20 – Polysorbate 20

PS80 – Polysorbate 80

QbD – Quality by design

QP – Qualified Person

NMR - Nuclear magnetic resonance

RH – relative humidity

RSD - Relative standard deviation

RSM - Regulatory starting materials

SST - system suitability test

TGA - Thermogravimetric analysis

THF - Tetrahydrofuran

TSE - Transmissible spongiform encephalopathy

UPLC - Ultra-high-performance liquid chromatography

USP – United States Pharmacopeia

USP/NF – United States Pharmacopeia/National Formulary

WFI – water for injection

XRD - X ray diffraction

XRPD - X-ray powder diffraction

UV – Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mundipharma GmbH submitted on 1 August 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Rezzayo, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure had been agreed upon by the EMA/CHMP on 25 March 2021.

Rezzayo was designated as an orphan medicinal product EU/3/20/2385 on 6 January 2021 in the following condition: treatment of invasive candidiasis.

The applicant applied for the following indication: *treatment of invasive candidiasis in adults*.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

At the time of submission of the application, the PIP P/0014/2019 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. New active substance status

The applicant requested the active substance rezafungin contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific Advice/Protocol assistance

The applicant received the following Scientific Advice/Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
20 September 2018	EMEA/H/SA/3888/1/2018/III	
28 February 2019	EMEA/H/SA/3888/1/FU/1/2019/III	
25 June 2020	EMEA/H/SA/3888/1/FU/2/2020/II	
24 June 2021	EMA/SA/0000061463	

The Scientific Advice/Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- *CMC development (regulatory starting material, stability, specifications)*
- *Nonclinical development strategy to support clinical studies and registration*
- *Need for a renal impairment study*
- *Agreement on the design of CD101.IV.3.05 (ReSTORE), pivotal study to support a MAA as a single pivotal trial for treatment of IC. More specifically agreement on the primary/secondary endpoints, population, comparator, rezafungin dosing regimen, non-inferiority margin, randomization scheme, sample size, statistical analysis plan, PK sampling*
- *Concurrence to include all subjects with a positive culture ⩽96 hours prior to randomisation in the primary mITT population in ReSTORE*
- *Overall safety database to support MAA*

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: Jayne Crowe

The application was received by the EMA on	1 August 2022
The procedure started on	18 August 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	8 November 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 November 2022

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	14 November 2022
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	29 November 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 December 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint AR on the responses to the LoQ to all CHMP and PRAC members on	29 June 2023
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	6 July 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	6 July 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report to all CHMP and PRAC members on	13 July 2023
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	20 July 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 September 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint AR on the responses to the LoOI to all CHMP and PRAC members on	27 September 2023
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report to all CHMP and PRAC members on	4 October 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Rezzayo on	12 October 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	12 October 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Invasive candidiasis includes both bloodstream and deep-seated invasive infections caused by *Candida* species. The infection generally occurs in patients whose immune system (the body's natural defences) has been weakened or when damage in body tissues allows the infection to spread like the elderly, post-surgical, post-transplantation and patients with other immunosuppressive conditions.

There are at least 15 distinct *Candida* species that cause human disease, but >90% of invasive disease is caused by the 5 most common pathogens, *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. Each of these organisms has unique virulence potential, antifungal susceptibility, and epidemiology, but taken as a whole, significant infections due to these organisms are generally referred to as invasive candidiasis.

Invasive candidiasis is a life-threatening disease that can be fatal due to damage to vital organs.

It has already been well established that any delay in initiation of appropriate antifungal therapy results in increased morbidity and mortality.

2.1.2. Epidemiology and risk factors

The annual incidence of candidaemia has been estimated as 7.4 per 100,000 population in the EU based on 23 published European studies after adjustment for Northern, Western, Central and Eastern European region. The reported candidaemia annual incidence ranged from 2.2 per 100,000 population in Portugal to 21.8 in Italy. Less published data is available for invasive candidiasis without identified candidaemia. A finding of 32.1% of patients with invasive candidiasis without candidaemia in French intensive care is supported by an estimate of 38% from a meta-analysis of post-mortem studies. An overall annual incidence for invasive candidiasis (with and without candidemia) can therefore be estimated at 10.9 per 100,000 EU population using the French data.

The prevalence of invasive candidiasis can be assumed to equal this incidence as invasive candidiasis is an acute condition with a duration of less than a year.

Over the past few decades, the incidence of IC has either progressively increased or remained stable in most regions of the world. This is probably due to the increasing complexity of surgical procedures and the growth of patient populations at higher risk of infection. At the same time, the increasing prevalence of multidrug-resistant organisms encourages the use of broad-spectrum antibiotics, which ultimately leads to selection of fungal infections.

The elderly and other highly vulnerable patient populations frequently have multiple comorbidities treated with numerous medications, increasing their risk of drug-drug interactions (DDI). Some antifungal agents, especially the azoles, have significant interactions with other drugs through the CYP3A4 pathway and the marketed echinocandins also have some interaction risk, especially with commonly used immunosuppressants and oncology drugs.

There are well-described risk factors associated with invasive candidiasis that apply to all hospitalized persons but especially to those in the ICU. Some risk factors are intrinsic to the host or the disease state, whereas others are the result of iatrogenic interventions. The most common individual risk factors include the presence of an indwelling central venous catheter, exposure to broad-spectrum antibacterial agents, long-term ICU stay with or without assisted ventilation, recent major surgery, necrotizing pancreatitis, any type of dialysis, total parenteral nutrition and iatrogenic immunosuppression.

2.1.3. Biologic features, aetiology and pathogenesis

When perturbations of mucosal microbiota and/or weakening of host immunity occur, *Candida* spp. transition from commensalism to opportunism, which is associated with the induction of key virulence factors. Specifically, there are three major conditions that predispose to human invasive infection:

- The first is long-term and/or repeated use of broad-spectrum antibiotics;

- Breach of the gastrointestinal and cutaneous barriers by cytotoxic chemotherapy-induced mucositis (inflammation of the mucosa of the gastrointestinal canal), gastrointestinal surgery or perforation and/or central venous catheters, which collectively enable commensal *Candida* spp. to translocate from mucocutaneous sites into the bloodstream;

- The third factor is iatrogenic immunosuppression, such as chemotherapy-induced neutropenia or corticosteroid therapy, which impairs innate immune defences in tissues and thereby facilitates *Candida* spp. invasion from the bloodstream into organs such as the liver, spleen, kidneys, heart and brain.

There are clinical strain-specific differences in fungal immune evasion and virulence. C. *albicans* secretes a variety of factors in the context of invasive infection, including secreted aspartyl proteases and phospholipases that activate the innate immune response but are also important for promoting fungal tissue invasion and organ damage. How the invasion of colonizing *Candida* spp. from the mucosa into the bloodstream and subsequent development of deep-seated infection occurs is not well defined. Effective adherence and invasion of *Candida* spp. in endothelial and epithelial cells enable their dissemination into the bloodstream. The capacity of *Candida* spp. for effective adherence also facilitates biofilm formation on implanted medical devices such as central venous catheters, which represents a major source of long-term candidemia.

2.1.4. Clinical presentation, diagnosis and prognosis

Invasive candidiasis refers to bloodstream infections with *Candida* spp. (that is, candidemia) and deep-seated infection — such as intra-abdominal abscess, peritonitis (inflammation of the peritoneum, the tissue that covers the inner wall of the abdomen and abdominal organs) or osteomyelitis (infection of the bones) — with or without candidemia.

Candida spp. colonization is regarded as a prerequisite for subsequent infection. *Candida* spp. are commensal yeasts that are part of the normal human skin and gut microbiota, and they are detectable in up to 60% of healthy individuals; thus, invasive disease is usually a consequence of increased or abnormal colonization together with a local or generalized defect in host defences.

Invasive candidiasis is not a single clinical entity but rather is a disorder with myriad clinical manifestations that potentially affect any organ, as each *Candida* sp. possesses its own unique characteristics relative to invasive potential, virulence and antifungal susceptibility. Overall, *C. albicans* is the most common pathogen in most clinical settings, but non-*albicans Candida* spp. collectively could represent >50% of the bloodstream isolates in certain regions.

The attributable mortality among all patients with candidemia has been reported to be between 10% and 47%, but a more-accurate estimate is probably 10–20%, with the risk of death being closely related to increasing age, higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, the infecting *Candida* sp. (for example, *C. parapsilosis* is less virulent than other *Candida* spp. and is generally associated with lower all-cause mortality), the use of immunosuppressive agents, pre-existing renal dysfunction and other comorbidities, venous catheter retention and specific antifungal treatment.

2.1.5. Management

In addition to early diagnosis, two clinical interventions are essential to the successful management of invasive candidiasis: source control and early initiation of treatment with early effective systemic antifungal therapy. Source control refers to the elimination of the suspected focus of infection, such as removal of contaminated intravascular catheters and effective drainage of collections of infected material, for example, peritoneal fluid, pleural fluid and/or abscess material.

The selection of an antifungal drug for initial treatment should be based on the patient's prior exposure or intolerance to an antifungal agent, severity of illness, relevant comorbidities and involvement of the brain, cardiac valves and/or visceral organs. The working knowledge of the main *Candida* spp. and susceptibility data in a particular clinical unit should also be considered. There are several published guidelines outlining expert recommendations for the management of invasive candidiasis and candidemia, with detailed recommendations for specific clinical circumstances. But we can say that most select an echinocandin (anidulafungin, caspofungin or micafungin) as first-line therapy for adult patients. Echinocandins are effective, safe and have very limited drug–drug interactions; however, they require intravenous administration. Also, the current ESCMID guidelines state that oral step-down therapy with fluconazole can be used to simplify treatment if the patient is stable, tolerates the oral route and if the species is susceptible. Other agents used to treat Candida infections include the azoles (fluconazole, itraconazole) and polyenes (amphotericin B products). The latter includes the lipid-based amphotericin products which were designed to reduce the pronounced toxicity of this drug, particularly the nephrotoxicity. However, Amphotericin B products are now largely confined to second or later line use in patients failing or refractory to echinocandins or azoles, except in chronic disseminated (hepatosplenic) candidiasis.

Rezafungin is a next-generation echinocandin derived from anidulafungin, designed to achieve improved chemical and metabolic stability and PK (longer half-life consistent with once weekly dosing). These adaptations, in turn, yielded multiple properties that differentiate rezafungin and potentially give patients and clinicians additional options beyond those of currently marketed antifungal agents.

Resistance in *Candida* spp. is either intrinsic (that is, found in all isolates within a species, such as fluconazole resistance in *C. krusei*) or acquired (that is, found in an isolate from a species that is normally susceptible,

such as echinocandin resistance in *C. glabrata*). Echinocandin resistance in *Candida* spp. is emerging, particularly in *C. glabrata*.

The target for the echinocandins is the β-D-glucan synthase enzyme, which is important for the cell wall synthesis. This enzyme is encoded by FKS1 in all *Candida* spp. and is also encoded by FKS2 in *C. glabrata*. Mutations in two hotspot regions (HS1 and HS2) of these genes have been identified as the underlying mechanism for echinocandin resistance, where the level of resistance is dependent on the position of the mutated codon (and the corresponding amino acid), the specific amino acid alteration (which amino acid replaces the original one) and in which species the mutation occurs. This increase in MIC as a direct result of FKS mutations has been identified as an independent risk factor for echinocandin failures in *C. glabrata* infections.

The need for new antifungal agents is underscored by pathogen-related trends in *Candida* species during the past 15 years.

2.2. About the product

Rezafungin is a next generation echinocandin. It selectively inhibits 1,3-β-D-glucan synthase, an enzyme present in fungal, but not mammalian, cells. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall. The synthesis of 1,3-β-D-glucan is dependent upon the activity of synthase complex, in which the catalytic subunit is encoded by FKS1, FKS2, and FKS3 genes. Inhibition of 1,3-β-D-glucan synthesis results in rapid and concentration-dependent fungicidal activity in *Candida* species (spp.). Rezafungin's spectrum of activity covers numerous fungal spp., including *Candida* spp., *Aspergillus* spp., *Pneumocystis* spp. and dermatophytes. Poor activity is observed for rezafungin against *Cryptococcus neoformans* and rare moulds (i.e., Mucorales, *Fusarium* spp., *Scedosporium* spp.), similar to that of other echinocandins.

2.3. Type of application and aspects on development

The initial clinical programme was designed to evaluate rezafungin for the treatment of patients with systemic infections caused by *Candida* spp.

The completed clinical development programme to support this submission consists of eight Phase 1 safety, pharmacokinetic (PK)/ pharmacodynamic (PD) and other clinical pharmacology studies in healthy subjects or special populations, together with the Phase 2 STRIVE and pivotal Phase 3 ReSTORE studies that evaluated the clinical safety and efficacy of rezafungin in the treatment of IC, including candidemia.

Phase 1 Studies

Clinical PK, dose escalation, and safety data in healthy subjects were collected at rezafungin IV doses of 50 mg to 400 mg (single dose) and 100 mg to 400 mg (multiple doses) in two controlled, randomised Phase 1 studies (single-ascending dose [SAD] study CD101.IV.1.01, multiple ascending dose [MAD] study CD101.IV.1.02; both completed), with a total of 56 subjects included. A controlled, randomised Phase 1 study to determine the effect of rezafungin on the QT interval in a total of 60 subjects also has been completed, providing rezafungin IV single dose PK data for up to 1400 mg (CD101.IV.1.06).

In addition, a Phase 1 photosafety study (CD101.IV.1.07) and an open-label Phase 1 DDI study (CD101.IV.1.09) have been completed, the latter including the following drug substrates that are known probes for a range of CYP drug metabolising enzymes and drug transporter proteins: tacrolimus, repaglinide,

metformin, rosuvastatin, pitavastatin, caffeine, efavirenz, midazolam, and digoxin. A second open-label Phase 1 DDI study (CD101.IV.1.17) has also been completed, which explored potential interactions with drugs which may be administered clinically with rezafungin: cyclosporine, ibrutinib, mycophenolate mofetil, and venetoclax.

To further determine the clinical PK characteristics of rezafungin and to assess the potential impact of hepatic impairment, a Phase 1 metabolism and excretion study in healthy subjects (CD101.IV.1.12), and a Phase 1 study in patients with hepatic impairment compared to healthy subjects have been conducted (CD101.IV.1.15), respectively.

Clinical Phase 2 and Phase 3 Safety and Efficacy Studies in IC

Phase 2 (STRIVE) was a controlled, randomised study, to assess two different dose levels of rezafungin versus the active control caspofungin IV, in subjects with C/IC. It enrolled 207 subjects in the ITT population (CD101.IV.2.03). The study was initiated in 3Q 2016 and completed in 2Q 2019.

The Phase 3 ReSTORE study, a multicentre, randomised, double-blind trial of the efficacy and safety of rezafungin versus the active control caspofungin IV, followed by optional oral fluconazole step-down, in the treatment of subjects with IC (CD101.IV.3.05) was initiated in 3Q 2018 and completed in 3Q 2021. Subjects were randomly assigned (1:1 ratio) to receive either rezafungin or caspofungin. A total of 199 subjects were enrolled into the ITT population.

The Phase 2 and Phase 3 studies had very similar designs including comparator, duration of dosing, dose levels and outcome measures. The results of the studies were also generally similar. The Applicant therefore believes that it is valid to submit a MAA at this time based on the single pivotal ReSTORE study supported by the STRIVE Phase 2 study. In line with the current guideline on the use of a single pivotal trial, the Applicant has analysed and presented data showing consistency within and across these studies and has presented pooled analyses of both the efficacy and the safety data.

The Applicant did not request Protocol Assistance following the orphan designation for rezafungin as the Phase 2 study was already complete and the Phase 3 study was at an advanced stage.

In Europe, rezafungin has also been the subject of Clinical Trial Applications to NCAs; a Paediatric Investigational Plan Application to EMA; and an Orphan Drug Application to EMA.

The CHMP noted that the clinical development programme was based in eight Phase I studies, one Phase II STRIVE and one Phase III ReSTORE study.

- The Phase II study STRIVE provided additional information for the dose selection for the Phase III trial. The primary endpoints chosen for the two trials are different as the primary objective of the Phase II study lacks the component of radiological cure; this precludes an integrated analysis for this endpoint (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-antifungal-agents-treatment-prophylaxis-invasive-fungal-disease_en.pdf; Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease) this advice was followed.

- After Scientific Advice, the use of ReSTORE as a single, pivotal study, with choice of caspofungin (plus optional oral fluconazole stepdown therapy) as the comparator was agreed. The primary objective is in accordance with Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease (CHMP/EWP/1343/01) and was changed from "All-cause mortality at Day 30" to "Demonstrate that rezafungin for injection is noninferior to caspofungin for global cure (clinical cure as assessed by the Investigator, radiological cure [for qualifying invasive candidiasis subjects], and mycological

eradication, as confirmed by the Data Review Committee [DRC]) at Day 14 (±1 day) in the mITT Population (European Medicines Agency [EMA] primary objective)"

- In its Scientific Advice, the CHMP /SAWP and other National Agencies involved noted that "meeting a 20% NIM in a single pivotal trial with an observed lower bound of the 95% CI that is >-20% but <-10% could result in an indication that is restricted to patients with limited treatment options".

- Pursuant to Article 22 of Regulation (EC) No 1901/2006, the applicant submitted to the European Medicines Agency on 19 April 2021 an application for a modification of the agreed pediatric investigation plan (EMEA-002319-PIP01-17-M01).

The PDCO adopted a favourable Opinion on the modification of the agreed PIP as set in the Agency's latest decision (P/0014/2019 of 3 January 2019):

The Non-clinical Working Group supported a deferral for the initiation of Study 2 based on the provided non-clinical data while awaiting the outcome of the ongoing studies. The proposal to request scientific advice regarding the JAS design is encouraged. As part of the request, the Applicant is advised to discuss the potential association of rezafungin-related phospholipidosis (PLD) and the observed tremors in monkeys. A new Study 2 completion date by March 2025 was proposed. The PDCO agreed to the proposed Study 2 timelines.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 200 mg of rezafungin (as acetate salt) as the active substance.

Other ingredients are: mannitol, histidine, polysorbate 80, hydrochloric acid and sodium hydroxide (for pH adjustment).

The product is available in a Type I clear glass vial closed with a chlorobutyl rubber stopper and sealed with an aluminium seal with a polypropylene flip-off cap.

2.4.2. Active substance

2.4.2.1. General information

The chemical name of rezafungin acetate is $N^{5.1}$,6-anhydro[(4*R*,5*R*)-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-(4*S*)-4-hydroxy-4-(4-hydroxyphenyl)-L-threonyl-L-threonyl-(3*S*,4*S*)-3-hydroxy-4-methyl-L-proline] acetate. It is a cyclic hexapeptide containing a quaternary ammonium side chain isolated as an acetate salt. Its relative molecular mass is 1285.46. The structure of rezafungin acetate is given below in ***Figure 1***:

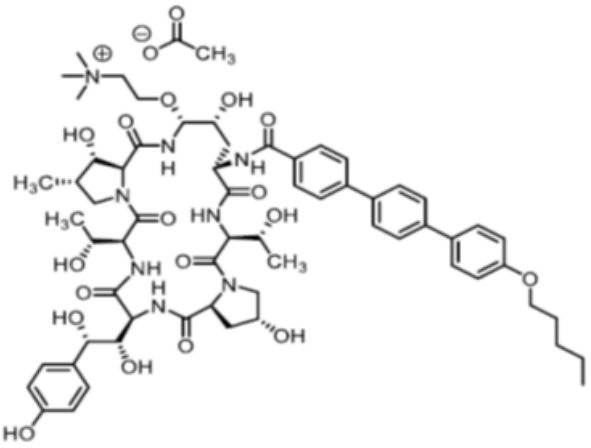


Figure 1. active substance structure

The chemical structure of rezafungin acetate was successfully elucidated with adequate methods, including proton nuclear magnetic resonance spectroscopy (^{1}H-NMR), carbon nuclear magnetic resonance spectroscopy (^{13}C-NMR), Fourier-transform infrared spectroscopy (FIR), UV-visible spectroscopy, high-resolution mass spectrometry and elemental analysis.

The properties of the active substance (AS) were also analysed by X-ray crystallography on ethanol/water solvate, X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and dynamic vapor sorption analysis (DVS).

Rezafungin acetate appears as a white to off-white amorphous hygroscopic solid. Solubility in a wide range of solvents have been described. Rezafungin acetate is water soluble.

Polymorphism and particle size are not of relevance, considering the nature of the finished product, i.e. lyophilised powder to be administered as a solution.

Rezafungin has 15 chiral centers which are defined during the fermentation process. The absolute stereochemistry of rezafungin acetate was confirmed by single crystal X-ray diffractometric analysis. The applicant confirmed that the stereoisomer with the presented structure was used in all the non-clinical and clinical studies and is the stereoisomer to be used in the commercial product.

2.4.2.2. Manufacture, characterisation and process controls

The AS manufacturers and their GMP status have been clearly stated.

Rezafungin acetate is manufactured using well defined starting materials with acceptable specification by a semi-synthetic process comprising fermentation followed by multiple chemical steps; the cell bank for the fermentation step is one of the starting materials. A thorough description of the synthesis of rezafungin acetate from the regulatory starting materials (RSMs) and detailed flow diagrams for each step with respective in-process controls were provided. The RSMs are controlled by acceptable specifications. The applicant has applied for EMA scientific advice regarding the selection of the RSM which have been considered acceptable since all principles of ICH Q11 are met. A manufacturing process with multiple proven acceptable ranges (PARs), but no design space, has been described in detail but was partly justified in the initial

submission. No development information has been initially provided to justify Stage 1 of the manufacturing process. This was raised as a Major Objection (MO) which was fully resolved with the responses (see below).

The information that was initially missing regarding the manufacturing process description (MO) was satisfactorily added to the dossier with the D120 responses. All the strains used in the fermentation process comply with Ph. Eur. Monograph 1468. The control and stability of the strains have been suitably described in the relevant sections of the dossier. The data provided shows that the quality of the strains is appropriately controlled.

All unit operations, such as reaction, workup, purification and isolation, are satisfactorily described for both stages of the process. Typical batch scale and yield were given for each step. Reprocessing steps have been satisfactorily described. There are no alternative processes described.

No materials of human or animal origin are used in the manufacture of rezafungin acetate. Acceptable specifications have been described for the solvents, reagents and auxiliary materials used in the stage 2 of the manufacturing process of the AS.
In-process controls and critical process parameters for the process along with appropriate controls of intermediates have been adequately described in the dossier and ensure sufficient control of the process. The parameters, specification and test methods used to ensure clearance of biological impurities of intermediates have been sufficiently described. As requested, relevant hold times for intermediates have been sufficiently specified and supported by data where relevant.

Although no specifications have been proposed for a process intermediate since it is not isolated, acceptable specifications for an intermediate downstream have been provided. Additionally, the in-process testing of the cell culture has been satisfactorily updated with the control of microbiological purity.

Critical process parameters (CPPs) and in process controls (IPCs) of Stage 2 of the manufacturing process of rezafungin acetate have been determined to ensure that the manufactured AS meets the established Critical Quality Attributes (CQA) outlined in manufacturing process development.

The relevant quality parameters in the synthesis of rezafungin acetate have been investigated during process development. The analytical methodology and acceptance criteria for the critical IPCs are sufficiently described and justified.

The specifications and analytical methods were provided for the control of the intermediates. The proposed acceptance limits for individual and total impurities in the specification of the intermediates have been satisfactorily justified.

The fermentation process has been satisfactorily validated as well as the critical synthetic steps. The overall information presented regarding the AS manufacturing process validation is in line with ICH M4Q(R1) and ICH Q11 and thus it is acceptable.

The development of the AS manufacturing process has been described. A description and justification of the changes made to the initial manufacturing process and its control strategy have been provided. A satisfactory summary of data and results with reference to AS used in preclinical and clinical studies was presented.
Based on the knowledge gained during the development studies and from production experience, the proven acceptable ranges (PARs), the normal operating ranges (NORs), and the critical process parameters (CPPs), were identified.

The process description has been updated during the procedure to describe a fixed process with set points or NORs. In addition, a tabulated list of identified PARs was provided for each step and it has been stated that

the flexibility of the relevant PAR can only be used one parameter at a time whilst the other process parameters remain within their respective NORs or set-point. The justification for the PARs and NORs, where appropriate, was provided in Section 3.2.S.2.6.

A satisfactory discussion on the impurities from starting materials, process-related impurities, inorganic and organic impurities, fermentation residues, reagents and solvents used in the manufacturing process was included. The origin, formation, fate, and control of those impurities (including potential mutagenic) was discussed in sufficient detail.

The proposed acceptance limits for the control of impurities were justified by impurity genesis, fate and experimental studies (purging studies), by batch analysis results and stability results. Specifically with regard to the potential formation and/or potential presence of nitrosamines in rezafungin acetate, the applicant's conclusion that the risk of nitrosamine formation or contamination is negligible and therefore no testing for nitrosamines in rezafungin acetate is required, was accepted, based on the presented risk assessment, justifications and experimental data.

The proposed control strategy generally complies with requirements of current ICH Q3A, Q3C, Q3D and M7 guidelines.

The active substance is packaged in a container complying with EU Regulations and relevant European Pharmacopoeia (Ph. Eur.) monographs. Specifications for the primary and secondary container closure have been presented and are deemed acceptable.

2.4.2.3. Specification

The active substance specification includes tests and limits for: appearance (visual), identification (NMR, HPLC), identification for acetate (HPLC), assay (HPLC), impurities (HPLC, UPLC), assay of acetate (HPLC), water content (KF), trifluoroacetate (HPLC), residual solvents (GC), bacterial endotoxin (Ph. Eur.) and bioburden (Ph. Eur.).

The active substance specification has been justified in accordance with the current EU regulatory requirements.

The proposed in-house specifications parameters comply with Ph. Eur. requirements for substances for pharmaceutical use. The proposed acceptance limits comply with the relevant ICH guidelines and derive from process knowledge and analytical results obtained on toxicology and clinical batches, and on regulatory and validation batches.

However, the current proposed limits for rezafungin assay and for individual and total impurities in the specification of rezafungin acetate could be tightened based on recent batch analysis results from release and stability studies, since a clear improvement in the impurity profile of the AS has been achieved during the development studies. Therefore, the CHMP recommended and the applicant has committed to revise and update the specifications accordingly after 20 commercial batches have been manufactured and released (Recommendation 2).

Bacterial endotoxins are controlled in the active substance intermediate and in rezafungin acetate according to Ph. Eur. 2.6.14. Potential microbial contamination in rezafungin acetate is controlled according to Ph. Eur. 2.6.12 and 2.6.13.

The analytical methods have been sufficiently described and successfully validated according to ICH Q2 guidance. However the CHMP recommended and the applicant has committed to update the system suitability test (SST) acceptance criteria for the analytical procedure "identification and assay of rezafungin acetate by HPLC" (Recommendation 1)**.** Besides, the stability indicating power of the analytical methods (i.e., specificity of methods in stress conditions/forced degradation studies) has been satisfactorily demonstrated.

Acceptable information was provided regarding the reference standards. The quality of the reference standards is considered acceptable for its use. Sufficient information regarding the reference standards used in the validation of analytical methods has also been provided.

Batch analysis data of 8 batches of AS manufactured at the propose site by the proposed commercial process (batches used for registration, stability studies, and process validation) comply with the current proposed specifications. These results indicate that the process is reproducible, is under control and confirm the consistency and uniformity of the active substance.

2.4.2.4. Stability

Stability data from four commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (-20°C ±5°C) and for up to six months under accelerated conditions (25°C ± 5°C/60% RH ± 5% RH) according to the ICH guidelines were provided.

Stability studies were also initiated on 3 process validation batches manufactured at the commercial site using the proposed commercial process. These studies are still ongoing; however, some available results are already presented (6 months at long-term and accelerated conditions). The post-approval stability protocol is acceptable.

The following parameters were tested for stability studies: appearance, assay, impurities, water content and microbial limits. As requested, the stability-indicating nature of the analytical methods was demonstrated.

Several chromatographic methods have been used to determine assay and process-related impurities in rezafungin acetate AS over the course of development and earlier stability studies. Also, water content method has been replaced by another equivalent method. A bridging study to demonstrate the equivalency of the methods has been provided, and the stability studies of the three process validation batches were updated with the available data, to confirm stability results obtained with the current analytical methods. All results comply with the specifications and are in line with the results for the four primary stability batches despite one out-of-trend (but within limits) result that has been observed in water content which is under investigation. Stability studies are still ongoing and will continue as committed by the applicant. No significant changes or trends were observed in any parameter on stability batches stored up to 36 months at long-term conditions and 6 months or 24 months (for earlier batches) at accelerated conditions.

Photostability testing following the ICH guideline Q1B was performed on a commercial scale batch. The photostability results indicate that rezafungin acetate packaged in only its primary packaging container is prone to light degradation. However, this degradation does not occur in rezafungin acetate packaged in its complete packaging system. The results of this study demonstrate that the packaging system selected for rezafungin acetate provides suitable protection from light exposure during storage, shipment, and handling. The storage conditions recommend protection from light.

The forced degradation results demonstrated that the methods are stability indicating.

Overall the stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container at storage condition of -20°C ± 5°C, protected from light.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The finished product (FP) is available as sterile lyophilized powder for reconstitution and dilution prior to intravenous (IV) infusion in a vial containing rezafungin acetate equivalent to 200 mg rezafungin free peptide. The lyophilised powder is reconstituted with 9.5 mL of water for injections to yield ≈10.5 mL of reconstituted solution that will be further diluted in appropriate infusion solutions prior to administration. The other ingredients include: polysorbate 80, mannitol, histidine, hydrochloric acid, sodium hydroxide and water for injection.

The pharmaceutically and clinically relevant physicochemical properties of the AS were duly identified, and are adequately specified and controlled.

All the excipients proposed are well-known pharmaceutical substances and compendial (Ph. Eur.). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Compatibility with excipients has been studied either as a single component or in combination with other excipients during formulation development. Studies indicate rezafungin is compatible with all excipients, which is further confirmed by the real time and accelerated stability data.

The FP development aimed to develop a sterile lyophilised product suitable for intravenous administration of rezafungin. The desired quality attributes were based in part on the existing knowledge of the commercially available echinocandin products and on the characteristics of the AS.

Formulation development followed a classical approach but a Quality Target Product Profile (QTPP) and critical quality attributes (CQA) for the drug product are provided, in line with ICH Q8 guideline. The history of formulation development through the different phases of clinical development has been presented. Description of the changes of formulation from clinical Phase 1 to Phase 3 formulations were duly provided.

The dosing regimen for Phase 3 studies included an initial dose of 400 mg and a subsequent dose of 200 mg, which is also the dosing regimen proposed for commercial use.

Manufacturing process development and optimisation extended from the initial development and implementation of the manufacturing process at the site for clinical supplies through to the technology transfer, process implementation and process validation at the site for proposed commercial supply.

The choice of manufacturing process has been justified. The choice of sterilization method has been addressed and is considered justified. The relevant Critical Process Parameters (CPPs) and In-Process Controls (IPCs) were addressed.

The lyophilised powder is packaged in a Type I clear glass vial closed with a chlorobutyl rubber stopper and sealed with an aluminium seal with a polypropylene flip-off cap. All packaging components are commonly used for parenteral drug products. Stability data support the compatibility of the container closure system with the formulation.

The compatibility of the FP with typical infusion solutions (0.45% NaCl, 0.9% NaCl and 5% dextrose) was determined on three pilot scale batches. All reconstitution solutions and diluted infusion solutions evaluated were stable with respect to the chemical and physicochemical parameters for up to 48 h of storage under room temperature or refrigerated storage conditions, demonstrating that the lyophilized powder is compatible with typical infusion solutions.

The microbiological stability of reconstituted and reconstituted and diluted FP was studied. It is recommended that FP solutions – reconstituted and reconstituted and diluted – are stored at 5±3 ºC if they are not to be used immediately (SmPC section 6.3).

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of the following 7 steps: preparation of solution; bioburden reduction filtration; sterile filtration; aseptic filling and partial stoppering; lyophilisation and stoppering of the dried vials; crimping; and visual inspection and storage. The process is considered non-standard manufacturing process.

A satisfactory narrative description of the manufacturing process was provided. During the manufacturing process development, potential CPPs were identified and IPCs were established to ensure a robust and reproducible manufacturing process.

Process validation has been performed on full-scale batches prior to commercial distribution. Validation included the relevant process parameters. The presented information addressed a MO raised by the CHMP in relation to the process validation data and its compliance with the relevant Guideline.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (UPLC , UV), water content (Ph. Eur.), reconstitution time, completeness and clarity of solution (visual), clarity and colour of solution (Ph. Eur.), assay (UPLC), degradation products (UPLC), uniformity of dosage units (Ph. Eur.), pH (Ph. Eur.), osmolality (Ph. Eur.), container content (Ph. Eur.), visible particulate matter (Ph. Eur.), subvisible particulate matter (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.).

The proposed specification is in line with Ph. Eur. and ICH guidelines. The proposed acceptance criteria in the specification are based on batches data, stability and process validation data.

The proposed specification limits have been satisfactorily justified considering the submitted batch and stability data. The proposed assay limit is wider that usual but had been justified on the basis of development and recent batches at the proposed site. However the CHMP requested and the applicant committed to revise the assay limit once 10 commercial FP batches have been manufactured (Recommendation 3).

A satisfactory summary of a risk assessment of the potential presence of elemental impurities in rezafungin acetate was provided in line with the ICH Q3D guidance.

The known and potential sources of elemental impurities that may find their way into rezafungin acetate were identified. The presence of individual elemental impurities in rezafungin acetate was assessed analytically and the obtained results were compared with the acceptable limits stated in ICH Q3D for the parenteral route of administration.

The approach adopted for elemental impurities is acceptable. Moreover, satisfactory information regarding the description and validation data of the analytical method (ICP-MS) used to test elemental impurities in the active substance has been provided, as requested.

Other inorganics have been tested and shown to be present in negligible levels in rezafungin acetate AS.

Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity control in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was presented. However, following a MO raised in this respect, it was updated considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020 Rev.12) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).

In response to this major objection the Applicant provided additional supportive data and a more comprehensive risk assessment to demonstrate the control of nitrosamine impurities in rezafungin finished product. Appropriate justification supporting the absence of confirmatory testing has been provided.

Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. However the CHMP recommended and the Applicant committed to update post authorisation the system suitability test (SST) acceptance criteria for the analytical procedure "Identification, Assay and Determination of Degradation Products" (Recommendation 4) .

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from development and commercial scale batches were provided. Batch analysis data from another 14 batches from the development site were also reported. All results complied with the proposed specifications.

2.4.3.4. Stability of the product

Stability data from 3 pilot scale batches of finished product manufactured by the development site, stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition stability data from 4 commercial scale batches of finished product, stored for up to 12 months under long term conditions and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were also provided.

Further supportive stability data from development batches stored up to 36 months under the same long term and accelerated conditions were provided.

Samples were tested for appearance, assay, impurities, water content, reconstitution time, appearance of reconstituted solution, clarity and colour of solution, pH, and sub-visible particulate matter and container closure integrity. The analytical procedures used are stability indicating.

No significant changes or evident trends have been observed. All reported results comply with the specifications.

Photostability testing was performed on one pilot batch, according to guideline ICHQ1B. The study demonstrates acceptable photostability for rezafungin powder for concentrate for solution for infusion, 200 mg/vial when stored in its secondary container.

Based on the overall stability data the proposed shelf life of the finished product (unopened vial) of 3 years and the proposed storage conditions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.4.3.5. Adventitious agents

No materials of human or animal origin are used in the manufacture of the finished product.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The Major Objections raised during the procedure concerning the description and overall control strategy of the active substance synthesis, the finished product manufacturing process validation and the nitrosamines risk assessment have been resolved by provision of additional data and information. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the revision of the specification limits for assay and for individual and total impurities for the AS and the revision of the specification limits for assay for the finished product and the system suitability test requirements for some analytical methods. These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to amend the AS system suitability test (SST) associated with the analytical procedure for the Identification and Assay of Rezafungin Acetate by HPLC, due June 2025;
2. The Applicant is recommended to review the AS specification (after 20 commercial batches have been manufactured and released) and tighten specification limits if supported by the accumulated batch data;
3. The Applicant is recommended to tighten the FP assay specification limits, once 10 commercial rezafungin drug product batches have been manufactured;

4. The Applicant is recommended to amend the FP system suitability test (SST) associated with the analytical procedure for the Identification, Assay and Determination of Degradation Products, due June 2025

2.5. Non-clinical aspects

2.5.1. Introduction

Non-clinical studies conducted with rezafungin include *in vitro* studies to confirm its mechanism of action, to identify its antimicrobial spectrum of activity and potency, and to establish *in vivo* efficacy in animal models of infection. Pharmacokinetic (PK)/toxicokinetic (TK) studies have been performed to determine the ADME properties of rezafungin. Studies have also been conducted to characterise its drug-drug interaction potential and establish the safety profile in pharmacology, safety pharmacology, general toxicology, genotoxicity, and developmental and reproductive toxicology studies.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Rezafungin powder for concentrate for solution for infusion (rezafungin) is a next-generation echinocandin for the treatment of invasive candidiasis (IC). It is structurally similar to currently approved echinocandins, a class of antifungals with an established mode of action and safety profile. The efficacy and safety of rezafungin (also previously referred to as CD101, AF-025, SP-3025 and biafungin) has been extensively evaluated using a variety of well-recognised *in vitro* and *in vivo* assay systems. The name "rezafungin" will be used hereafter.
1,3-β-D-glucan is an essential component of fungal cell walls. Its synthesis is dependent upon the activity of 1,3-β-D-glucan synthase, an enzyme complex in which the catalytic subunit is encoded by *FKS1*, *FKS2*, and *FKS3* genes. Echinocandins, including rezafungin, inhibit the 1,3-β-D-glucan synthase enzyme complex.

The *in vitro* activity of rezafungin has been profiled throughout development using Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI M27, 2017; CLSI M38, 2017). These studies were conducted prior to the availability of a European Committee on Antimicrobial Susceptibility Testing (EUCAST)-approved standard susceptibility testing method. A multicentre study, co-ordinated by EDL, was then conducted to determine rezafungin MICs against clinical Candida isolates from the six most common species using the EUCAST reference method, E.Def 7.3.2, modified to include Tween 20 at a final concentration of 0.002% to mitigate the impact of non-specific compound binding (EDL Multi-centre study). Applicant claims that this modification provides an acceptable reference susceptibility testing methodology for rezafungin. However,

the effect of Tween 20, at the concentration of 0.002%, on Candida strains' permeability to rezafungin as well as on the stability of biofilms, with the consequent impact in rezafungin MIC, has not been tested. On the other hand, modification of the standard reference testing methodology, whilst generally not preferred, is accepted by both EUCAST and CLSI to mitigate against non-specific binding. While both PS80 and T20 have been shown to inhibit *E. coli*, *P. aeruginosa* and *S. aureus* biofilms *in vitro,* at sub-micromolar concentrations, without a negative impact on growth, the Applicant has not been able to find any publications that examined the effect of polysorbates on the stability of fungal biofilms. Nevertheless, in the context of susceptibility testing, after the various culturing stages required to purify and identify the organism, and the preparation of the inoculum for testing, isolates are not expected to be associated with biofilms. Therefore, it may be accepted that an effect of T20 on biofilms (if any) will be irrelevant to the determination of rezafungin MIC.

Rezafungin is a potent inhibitor of *Candida* spp. demonstrating rapid, fungicidal activity, *in vitro* activity against *Candida albicans* growing in biofilms, and a low propensity to induce resistance development.

While the echinocandin class is not fungicidal against moulds, rezafungin does show potent *in vitro* growth inhibition activity against *Aspergillus* spp. including azole-resistant strains, dermatophytes such as *Trichophyton mentagrophytes*, *Trichophyton rubrum*, and *Microsporum gypseum*, as measured by the minimum effective concentration (MEC) assay. Rezafungin also shows *in vitro* activity against *Pneumocystis jirovecii* (previously known as *Pneumocystis carinii*) suspension and biofilm cultures.

A series of studies in the neutropenic mouse systemic candidiasis model shows that rezafungin is efficacious when administered by either the intravenous (IV) or intraperitoneal (IP) routes. A study in a *Pneumocystis murina* pneumonia treatment model showed that rezafungin can also be used to treat *Pneumocystis* infected mice.

Rezafungin was also found to be protective (prophylactic) against fungal challenge in prophylactic mouse models of candidiasis, aspergillosis, and *Pneumocystis* pneumonia suggesting that rezafungin may provide benefit as antifungal prophylaxis in patients at risk for infection.

2.5.2.2. Secondary pharmacodynamic studies

Secondary pharmacodynamic (PD) effects were evaluated using *in vitro* inhibition of ligand binding and enzyme activity for a panel of targets (NC-046). Rezafungin interfered with binding of nearly all of the ligand targets, suggesting that the physicochemical properties (cationic and amphipathic) were not compatible with these assays. However, there was no inhibition or stimulation of >25% in any of the enzyme activity assays, a more relevant method for evaluating off-target activities for an agent whose mechanism is based upon enzyme inhibition. Subsequent testing of rezafungin in functional assays (NC-182) of central nervous system (CNS)-related targets showed that most agonistic or antagonistic interactions were in the high micromolar range with a few single digit ones such as β1 antagonism IC_{50} (50% inhibitory concentration) of 9.09 µM or the dopamine transporter uptake IC_{50} of 2.93 µM. These *in vitro* results are unlikely to be physiologically relevant as maximum total clinical plasma concentrations (total C_{max}) achieved are approximately 22.7 mg/L, which equates to about 0.59 mg/L or 0.48 µM free C_{max} concentration (assuming PPB of 97.4%) and only briefly at the end of IV infusion of a 400 mg rezafungin dose. The significant off-target effects detected from the binding assay and the expected *in vivo* outcomes, were further discussed in an integrated approach with the results obtained in safety pharmacology and toxicology studies. The findings of the studies investigating the cardiovascular, respiratory, CNS and toxicology effects of rezafungin, indicate that the off-target activity identified *in vitro* does not translate to *in vivo* effects. The nonclinical safety profile is consistent with the poor

intracellular penetration — very low apparent permeability (P_{app} AB 0.019, P_{app} BA 0.012 (10^{-6} cm s^{-1})) values obtained in a permeability assay using Caco-2 epithelial monolayers and poor brain penetration of rezafungin.

2.5.2.3. Safety pharmacology programme

Rezafungin was assessed in core battery safety pharmacology evaluations for effects on neurobehavioral, cardiovascular (haemodynamic and electrocardiographic [ECG]), and respiratory functional endpoints. There were no clinical 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 (NC-025).

Two *in vitro* human ether-à-go-go-related gene (hERG) studies (screening [NC-045] and pivotal [NC-060]) and a Good Laboratory Practice (GLP) combined cardiovascular and respiratory study (NC-059) in cynomolgus monkeys were conducted. In the *in vitro* screening and pivotal studies, rezafungin had no effect on hERG current, relative to vehicle alone, when tested up to the maximum concentration able to be evaluated of 1.0 µM, half maximal inhibitory concentration (estimated IC_{50}) values were >1 µM. In the pivotal study, rezafungin did not affect hERG current up to a concentration of 1.1 µM, the maximum concentration able to be evaluated, which exceeds the estimated free drug C_{max} in the clinic. At a total C_{max} plasma level of 22.7 mg/L in humans following a 400 mg dose (clinical Phase 1 study CD101.IV.1.01), the free drug C_{max} plasma level is 0.48 µM (assuming PPB of 97.4%), which is 2.3-fold lower than the maximum concentration tested in the hERG assay.

Administration of a 20 minute IV infusion of rezafungin to telemetered male cynomolgus monkeys (NC-059), did not cause changes in body temperature, blood pressure, ECG and respiratory parameters at doses up to 10 mg/kg, but there was a minimal and transient decrease in heart rate relative to vehicle control in restrained cynomolgus monkeys at ≥3 mg/kg that was of uncertain relationship to rezafungin.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interactions studies were not performed, which was accepted by the CHMP.

2.5.3. Pharmacokinetics

The PK profile of rezafungin in plasma was investigated in mice, rats, rabbits, dogs, cynomolgus monkeys, and chimpanzees by the IV route. Rezafungin has also been administered IP to mice and rats, IM to rats, SC to rats and cynomolgus monkeys, and orally to dogs, monkeys, and chimpanzees.

Biological samples were obtained in nonclinical PK and toxicokinetic (TK) studies aimed at measuring rezafungin concentrations. Concentrations were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). These 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 K3EDTA [tri-potassium ethylenediaminetetraacetic acid]) from rats (NC-050) and monkeys (NC-051) as part of TK 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 U.S. Code of Federal Regulations Title 21 Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

Across all species tested administered by the IV route, rezafungin consistently exhibited very low clearance, modest volume of distribution, and long $t_{1/2}$. Generally, high bioavailabilities (>70%) were observed from IP, SC, or IM administrations but oral dosing resulted in low oral bioavailability (2 to 12%). Exposure to rezafungin was generally dose-proportional with no apparent sex differences, and, depending on frequency of dosing, moderate accumulation was noted after repeated administrations. Rezafungin exposures were also comparable in normal (uninfected) and *Candida*-infected mice, in which translational efficacy models were carried out.

Like other echinocandins, protein binding of rezafungin is high across different animal species and humans, but it appears to be higher in mouse (primary animal efficacy model) than in human plasma. The range of protein binding values were 99.2 to 99.3% (mean or median = 99.2%) in mouse plasma and 96.4 to 98.0% (mean or median = 97.4%) in human plasma. Corresponding mean (or median) % free-drug values were 0.8% and 2.6% in mouse and human plasma, respectively.

Tissue distribution was evaluated in rats after IV administration of rezafungin, demonstrating widespread exposure in various organs, with tissue/plasma AUC ratios that were comparable (approximately 4-fold higher in tissue than plasma) for major (kidney, lung, liver, spleen) organs with the exception of the heart and brain. Subsequent studies in rats and monkeys with [^{14}C]-radiolabelled rezafungin confirmed the extensive tissue distribution as well as long-lived radioactivity detectable in nearly all tissues following a single IV dose administration.

Mouse lung ELF exposure (from BALF) was also compared to plasma and based on AUC exposure ratios of ELF/plasma, the distribution of rezafungin from plasma into lung ELF is close to unity (0.80 and 0.95 based AUC_{last} and AUC_{inf}, respectively) suggesting good penetration into site of infection. In another site of infection study, the spatial and quantitative distribution of rezafungin was compared to micafungin in tissue lesions in a clinically relevant, IAC mouse model. Although drug accumulation within lesions was observed with both drugs at their humanised therapeutic doses, rezafungin demonstrated superior penetration and concentration at the site of the abscess versus micafungin. Rezafungin, but not micafungin, accumulated in lesions at levels above the mutant prevention concentration of the infecting strain.

A placental transfer study was deemed unnecessary by the Applicant as the pre- and postnatal development study in rats (NC-172) already provides evidence that rezafungin crosses the placenta. Based on the nonclinical lines of evidence, the Applicant considers that the placental transfer of rezafungin has no impact on foetal development. However, its clinical significance is currently unknown as clinical studies with rezafungin have not been conducted in pregnant women. A statement has therefore been included in the RMP stating that information of pregnancy/breastfeeding is missing. A statement has also been included in SmPC Section 4.6 stating that rezafungin crosses the placental barrier in animals, but the potential risk to humans is unknown. The statements in SmPC Section 5.3 also describe effects following placental transfer in animals.

In vitro, rezafungin was stable across species after incubation with liver and intestinal microsomes and with hepatocytes, suggesting little or no biotransformation, and comparative metabolite profiling experiments yielded no identifiable metabolites. Rezafungin when incubated in phosphate buffered saline is chemically stable, with no evidence of formation of reactive intermediates. *In vivo*, [^{14}C] rezafungin dosing studies in the rat and monkey were able to detect the presence of a few low level and relatively inactive metabolites, namely, hydroxylation of the terphenyl, pentyl ether group of rezafungin and loss of the pentyl group via O-dealkylation.

An initial study in rats administered a single IV dose of rezafungin determined that excretion of unchanged drug into faeces was the predominant route of excretion. The mean cumulative amount of rezafungin excreted into the bile and faeces over the course of 5 Days accounted for approximately half of the total dose

administered. Subsequently, studies were conducted in SD rats as well as in cynomolgus monkeys using [^{14}C]-radiolabelled rezafungin to characterise the rate and extent of excretion (mass balance) of total radioactivity in urine, faeces, and bile (rat only) following a single intravenous (IV) dose of [^{14}C] rezafungin. These studies confirmed that the main route of excretion from an IV administration was nonrenal, primarily via the faeces. Excretion in bile was roughly half of the amount of radioactivity excreted in faeces of bile duct cannulated rats, indicating direct intestinal secretion of rezafungin is likely.

Rezafungin did not cause inhibition of human CYP isoforms (1A2, 2B6, 2C9, 2C19, and 2D6). Inhibition of CYP2C8, and 3A4 was observed, but only at high concentrations (IC_{50} values of >25 µM) relative to unbound C_{max} following 400 mg dose in the Phase 1 Study CD101.IV.1.02 of 0.5 µM, suggesting effects are unlikely to be observed clinically. Rezafungin was not a time-dependent inhibitor of the same 7 major human CYP isoforms when tested up to its solubility limit of 25 µM. Using hepatocytes from 3 separate donors, no evidence of CYP induction (as measured by <2-fold increase in mRNA expression) of CYP1A2 and CYP2B6 and, in the case of CYP3A4, in 2 of 3 donors. More specifically, for CYP3A4, only 1 out of the 3 donors tested showed a 2.68-fold induction of mRNA expression at the highest feasible concentration (3 µM) tested.

Rezafungin was also found not to be a substrate for the following transporters: MDR1 (P-glycoprotein; P-gp), BCRP, MRP2, OATP1B1, OATP1B3, OCT1, OCTN1, or OCTN2. Rezafungin was determined to be an inhibitor of transporters P-gp, OATP1B1, OATP1B3, OAT1, OCT2, OCT1, MATE1, and MATE2-K, but not BCRP, OAT3, or BSEP. Clinical studies confirmed that the need for dose adjustments is considered unlikely for drugs that are substrates for the cytochrome P450 enzymes CYP3A, CYP2C8, CYP2B6, and CYP1A2, and the drug transporter proteins P-gp, BCRP, OATP, OCT1, OCT2, MATE1 and MATE2, when administered with rezafungin.

Overall, the absorption, distribution, metabolism, and excretion profile of rezafungin observed in non-clinical studies, showing low clearance, a long half-life (generally >30 hrs), widespread penetration into tissues, minimal biotransformation, and extensive excretion as unchanged drug, supports its intended clinical use as a once-weekly IV therapy.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single dose toxicity studies comprised two studies in Sprague-Dawley rats and two in cynomolgus monkeys. In these studies, none of which were GLP-compliant, rezafungin was administered by the intravenous route at different rates (from slow IV bolus up to 60 minutes IV infusions) and using different vehicles – none of which fully corresponds to that of Rezzayo. In the two studies in rats, one of which lacked a negative control group, the animals were observed for up to 3 days post-dose and subjected to gross necropsy. In one of the studies in monkeys, the animals were observed for up to 3 days post-dose; in the other, for up to, at least, 13 days. In none of the studies in monkeys, the animals were sacrificed. Instead, in the study with observation during up to, at least, 13 days, the monkeys were also examined for effects on clinical pathology parameters (haematology and serum chemistry) and for toxicokinetics.

None of the studies revealed mortality up to the highest tested doses (up to 60 mg/kg by slow IV bolus, 50 mg/kg by 10-min IV infusion, or 30 mg/kg by 20-min or 60 min IV infusion). The studies in rats showed transient clinical signs of systemic toxicity (at ≥ 20 mg/kg by 20-min IV infusion or by slow IV bolus) and irritation at the site of administration. Regarding the studies in monkeys, one showed change in clinical pathology parameters from pre-dose values and the other the occurrence of slight tremors during the infusion.

Also supported by the results of a mechanistic study, the transient clinical signs of systemic toxicity observed in rats were attributed to an acute histamine release response. Furthermore, it was considered that the rat histamine-release response was consistent with the observation for several marketed echinocandins which demonstrate rats to have an enhanced sensitivity to this histamine-release response relative to monkeys, dogs, and humans.

The findings in monkeys were, in any case, also present in the control groups, which received vehicle only. In the study in monkeys with toxicokinetic analysis, systemic exposures (based on Cmax and AUC0-t values) at the highest tested dose (NOAEL) were approximately 4-6 times higher than those expected in patients.

2.5.4.2. Repeat dose toxicity

Repeated dose toxicity studies were conducted in Sprague-Dawley rats and cynomolgus monkeys and comprised 5 non-pivotal studies, with treatment durations of up to 4 weeks, and 6 pivotal studies, GLP-compliant, with treatment durations, in both animal species, of 4, 13 and 26 weeks. All the studies were conducted with administration by the intravenous route. In the pivotal rat studies, this was by slow intravenous bolus; in the pivotal monkey studies, by 20- to 60- min intravenous infusions. All pivotal studies included recovery periods; these were of 6 or 12 months duration in the 26-week studies in rats and cynomolgus monkeys, respectively. The vehicles used in the pivotal studies in rats and monkeys differed in terms of the concentration of tween 80 – 2.5% in studies in rats and 1.15 or 0.5% in studies in monkeys. Monkeys employed in the 26 -week study were sexually mature.

The choice of rats and cynomolgus monkeys was justified by the Applicant. The rat is a widely used animal species and already used to evaluate toxicity of the marketed echinocandins, and, furthermore, adequate plasma exposure was attained. Cynomolgus monkeys were chosen as the nonrodent toxicology species due to similar in vitro metabolic stability and protein binding characteristics to humans and because monkeys have been shown to be predictive for echinocandin-induced toxicity in humans.

Rats

In the 4- and 13-week rat pivotal studies, the animals received rezafungin every 3 days at 0, 5, 15, 30 or 45 mg/kg/dose. In the 26-week study, rezafungin was administered once weekly at 0, 10, 25, or 45 mg/kg. In the three studies, the vehicle used was Tween 80, mannitol, acetic acid, pH 4.5.

In the 4- and 26-week repeated dose toxicity studies, in addition to conventional repeated dose toxicity endpoints, the animals were also examined for effects on specific central nervous system safety pharmacology endpoints, including functional observational battery (FOB) parameters. Furthermore, the 26-week study also included a detailed survey of nerve tissue from peripheral and central nervous system.

In the longest-term study, the 26-week study, there were no rezafungin-related deaths. There were no rezafungin-related effects on food consumption, coagulation, urinalysis, or organ weights. There were no rezafungin-related FOB, ophthalmic, or macroscopic examination findings. Administration of rezafungin resulted in non-adverse transient histamine-mediated clinical observations noted in the 10, 25, and 45 mg/kg group males and females throughout the dosing period that decreased in incidence after the first 9 weeks. Rezafungin-related non-adverse lower body weight gains were noted in the 25 mg/kg group males and females and the 45 mg/kg males generally throughout the dosing period, but were comparable to the control group throughout the 26-week recovery period. Rezafungin-related changes in haematology (increased platelet counts) and clinical chemistry (increased alanine aminotransferase activity) parameters, which lacked

microscopic correlates, were noted in the 45 mg/kg group males with complete reversibility at the recovery evaluation.

None of the rezafungin-related changes in either the Main Study or Recovery Study animals were interpreted to be adverse due to their transient nature, low magnitude of change, and severity observed. Based on these results, the NOAEL was considered to be 45 mg/kg. This dose corresponded to mean AUCtlast values of 3560 and 2940 µg·hr/mL and mean Cmax values of 290 and 251 µg/mL for males and females, respectively, on Day 176.

The NOAEL for local vascular injury was determined to be 30 mg/kg/dose.

Systemically, effects considered to be adverse were limited to those attributed to transient acute histamine response. Other effects, namely, changes in clinical pathology parameters and histological findings in male reproductive organs and in spleen were not considered to be adverse based on their magnitude and reversibility. The NOAEL for transient acute histamine-mediated effects was determined to be 5 mg/kg/dose; the NOAEL for other systemic effects was 45 mg/kg/dose, the maximum tested dose.

Effects observed in the 4-week study which were additional to those observed in the 13-week study were limited to an increase in blood urea nitrogen, at 45 mg/kg/dose, and minimal alveolar histiocytosis (≥ 15 mg/kg/dose). There were no effects on body temperature or FOB parameters.

Cynomolgus monkeys

In the 4- and 13-week studies, animals were treated once every 3 days and the used vehicle was Tween 80, mannitol, acetic acid, pH 4.5. In the 4-week study, animals received rezafungin by 20-minute IV infusion at 0, 3, 10 or 30 mg/kg/dose. In the 13-week study, the tested dose levels were 0, 3, 10, 30, 60/45 mg/kg, with the highest dose reduced from 60 to 45 mg/kg at Day 42. The mode of administration was by IV infusion for 20 up to 40 minutes, depending on the dose level. In the 26-week study, rezafungin was administered once weekly at 0, 5, 15, or 30 mg/kg; the vehicle used was Tween 80, mannitol, acetic acid, pH 4.5.

In the 13-week study, in addition to conventional repeated dose toxicity endpoints in non-rodent studies, animal examination included a detailed neuropathology assessment. In the 26-week study, animals also underwent neurobehavioral assessments (dosing/cageside observations and veterinary neurological examinations), nerve conduction measurements, testicular volume, and sperm evaluations. Furthermore, the 26-week study was partially blinded. The individuals performing mortality observations, clinical observations (cage side, detailed, injection site and unscheduled observations), veterinary neurobehavioral examinations, body weights, food consumption evaluation, dose administration, ophthalmic examinations, electrocardiology collections/measurements, nerve conduction measurements/calculations, testicular volume measurements, sperm collection/analysis, clinical pathology and bioanalytical blood collections, necropsies, and macroscopic examinations were unaware of the dose group designations.

In the 26-week study, there were injection site reactions on the tail noted in several animals at 15 and 30 mg/kg. There were no other rezafungin-related clinical observations. There were no rezafungin-related effects on survival, body weight, food consumption, coagulation, clinical chemistry, urinalysis, or electrocardiology. There were no rezafungin-related ophthalmic, neurobehavioral, macroscopic findings or effects on reproductive organs or sperm parameters. Neuro-electrophysiological evaluations (neurography) demonstrated sensory and motor nerve conduction remained within functional physiological ranges at all timepoints (Weeks 13, 25, and 53). Throughout the study, generalized tremor observations were noted in all

groups (including controls) by the technical staff during the dosing procedure and by the veterinarian during the neurobehavioral examinations. The technician generated data and the veterinarian generated data both demonstrated no dose- or time-related trends in the numbers of tremors, nor in the severity of tremors, and thus there is no indication of a rezafungin-related tremor finding.

The NOAEL for systemic toxicity was considered to be 30 mg/kg. This dose corresponded to mean AUCtlast values of 4630 and 4080 µg·hr/mL and mean Cmax values of 154 and 165 µg/mL for males and females, respectively, on Day 176.

In the pivotal 13-week study, high dose females showed increased incidence and severity of neurobehavioral findings (i.e., tremors, intention tremors) and a declining condition (e.g., hunched posture, thin body condition, dermal atonia, decreased defecation, labored respiration, and/or unkempt appearance) of 2 female animals. In surviving animals, clinical signs of toxicity included tremors and/or intention tremors at all dose levels, with higher incidence at ≥ 30 mg/kg/dose, and piloerection (all doses). There was a slight decrease in heart rate (≥ 30 m/kg), changes in clinical pathology parameters, namely, increase in platelets (≥ 30 m/kg), decrease in MCHC (≥ 30 m/kg), increase in ALT and AST (≥ 10 mg/kg), sorbitol dehydrogenase, calcium (≥ 30 mg/kg), urea nitrogen and potassium (60/45 mg/kg) and increase in ionised calcium (≥ 30 mg/kg). Histopathological changes were observed in the dorsal root ganglion and peripheral nerves, with an increased incidence of intracytoplasmic inclusions within Schwann cells (all doses), increase cellularity of Schwann cells and myelin sheath thinning (≥ 30 mg/kg). Axonal degeneration was observed in two males 60/45 mg/kg. Following the primary necropsy, one male had severe axonal degeneration of multiple fascicles in the right sciatic nerve; following the recovery necropsy, another male had moderate axonal degeneration in the left sural nerve of a T blue-stained resin section. Ultrastructurally, the Schwann cell inclusions were considered to be consistent with lysosomal accumulation of membranous material, a portion or majority of which may have been incompletely degraded myelin. Schwann cell inclusions were still present 4 weeks later at the recovery necropsy at a level similar to the primary necropsy in the 30 and 60/45 mg/kg/dose groups. Increased cellularity was partially recovered.

The NOAEL was determined to be 30 mg/kg/dose. The findings on decreased heart rates and changes in clinical pathology parameters were not considered adverse, due to their magnitudes. The tremors/ intention tremors did not interfere with the daily normal function of the animals. The Schwann cell changes were considered an adaptive response and non-adverse.

Tremors were also observed in the pivotal 4-week study in cynomolgus monkeys at the highest tested dose (30 mg/kg), as well as in the non-pivotal 2-week study at both tested doses (10 and 30 mg/kg).

In both animal species, systemic exposures in the pivotal repeated dose toxicity studies increased with dose levels, showed no major gender effect (no significant differences between males and females) nor accumulation upon repeated dosing. There were no measurable rezafungin concentrations in plasma samples from the control animals.

According to the provided calculations of exposure multiples, in the longest-term repeated dose toxicity studies (26-week), systemic exposure at the determined NOAEL in monkeys (30 mg/kg) was nearly 6-fold that expected in patients, based on AUC0-168hr; at the NOAEL in rats (45 mg/kg) was nearly 4-fold that expected in patients.

2.5.4.3. Genotoxicity

Rezafungin was not genotoxic in a standard battery of assays, including an in vitro mammalian cell mutation assay, an in vitro clastogenicity assay, and an in vivo rat bone marrow micronucleus assay.

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been conducted. Considering the proposed therapeutic indication and the proposed duration of treatment, this was considered a satisfactory approach.

2.5.4.5. Reproductive and developmental toxicity

Reproductive toxicity studies comprised studies on fertility and early embryonic development (Sprague Dawley rats), embryo-fetal development (Sprague Dawley rats, New Zealand White rabbits) and pre and postnatal development (Sprague Dawley rats). Fertility and early embryonic development studies included two separate studies, one on female and the other on male fertility. The studies on embryo-fetal development were preceded by pilot/dose range-finding studies. Except for part of these pilot/dose range-finding studies, all other reproductive toxicity studies were GLP-compliant.

Fertility and early embryonic development

In the separate male and female fertility and early embryonic development, rezafungin was administered by slow intravenous bolus injection once every 3 days in Tween 80, mannitol, and acetic acid, pH 4.5. The tested dose was 0, 5, 15, and 45 mg/kg/dose, in females, and 0, 15, 30, or 45 mg/kg/dose, in males. In addition to the routine parameters, the males were also submitted to a spermatogenic evaluation.

The studies revealed no effects on reproductive performance or intrauterine parameters.

There were no effects found in testis or epididymides weights, sperm concentration in the testes, or sperm production rate. However, there was a decrease in sperm concentration in the left cauda epididymis (45 mg/kg), sperm motility (≥30 mg/kg), an increased incidences of sperm with abnormal morphology (normally shaped head separated from the flagellum and head absent with normal flagellum [≥30 mg/kg]), degeneration of the seminiferous tubules within the testes (≥30 mg/kg) and cribriform change in the epididymides (≥30 mg/kg). Results from a detailed stage-specific histological analysis suggested that the effect occurred on the later stages of spermatogenesis (i.e., spermiation).

Based on toxicity findings in agreement to those observed in repeated dose toxicity studies, the NOAEL for general toxicity in the female and male studies were determined to be 5 and < 15 mg/kg/dose, respectively. The NOAEL for effects on female fertility and, upon treatment of either females or males, early embryonic development was set at 45 mg/kg/dose, the highest tested dose. The NOAEL for male reproductive toxicity was determined to be 15 mg/kg. Based on human exposure data and animal toxicokinetics data extrapolated from the 4-week repeated dose toxicity study, there is a low safety margin (2-fold, based on AUC) for the effects observed in male reproductive organs. Exposure multiple at 45 mg/kg is estimated to be 6.3, based on AUC.

Embryo-fetal development

In the pivotal embryo-fetal development studies, rezafungin was administered by slow IV bolus injection, once every 3 days and using the vehicle Tween 80, mannitol, and acetic acid, pH 4.5. In terms of dose levels and treatment periods, rats received 0, 5, 15, 30, 45 mg/kg/dose from 1 week prior to mating until gestation

day 17 - 1 week prior to mating with the aim of ensuring sufficient systemic exposure by implantation (GD6) and to minimise potential confounding effects of the rat-specific early and transient histamine-release response-; rabbits were administered 0, 5, 15, 35 mg/kg from gestation day 7 up to gestation day 19. Both studies included toxicokinetic analysis.

In both pivotal studies, there were no effects on intrauterine growth and survival and foetal morphology. The NOAEL for embryo-fetal development were therefore determined to be the maximum tested dose in each study - 45 mg/kg/dose in rats and 35 mg/kg/day in rabbits. Based on AUC values, these doses represent safety margins of 4.7 and 3.2, respectively. Regarding general toxicity, the NOAEL in rats was < 5 mg/kg/dose and in rabbits 35 mg/kg/dose.

Pre- postnatal development

In the pre-postnatal development, rezafungin was administered by slow IV bolus injection every 3 days at 0, 5, 15 or 45 mg/kg/dose from 1 week prior to mating up to lactation day 20. The study included measurement of concentrations of rezafungin on maternal and fetal plasma at 1-hour post-dose on gestation days 18-20 and on maternal plasma and milk at 1-hour post-dose of lactation days 8-10.

The study revealed no effects on pre-and postnatal development up to the reproduction of the F1 generation, and, therefore, the NOAEL for pre- and postnatal development was set at 45 mg/kg/day. At this dose, based on human exposure data and animal toxicokinetics data extrapolated from the pivotal rat embryo-fetal development study, maternal systemic exposure based on AUC was estimated to be nearly 5-fold the exposure in patients.

In terms of general toxicity, there were clinical observations associated with the expected early histamine-release response, at all dosage levels. These were not considered adverse, given their transient nature. The NOAEL for general toxicity was also set at 45 mg/kg/dose.

At 1-hour post-dose, on gestation days 18-20, concentration of rezafungin in fetal plasma was 1.9 – 3.6% the concentration in maternal plasma; on lactation days 8-10, concentration of rezafungin in the milk was 22-26% that found in maternal plasma.

2.5.4.6. Local tolerance

Perivascular, intramuscular, and subcutaneous injection of rezafungin, using the clinical formulation, to male rabbits produced no adverse gross and microscopic findings and results were comparable to placebo-treated injection sites.

2.5.4.7. Phototoxicity

As with other echinocandins, rezafungin absorbs light in the UVA/UVB range and thus an in vitro phototoxicity assessment was conducted in 3T3 fibroblasts. Rezafungin, like anidulafungin, induced a positive response in vitro. Rezafungin was also tested for phototoxicity potential in rats where a dose-related minimal phototoxic response was observed at Cmax plasma concentrations ≥6.9-fold above those achieved clinically following 400 mg loading dose. A Phase 1 study in healthy volunteers indicated that subjects who receive 400 mg rezafungin once weekly are at a mildly increased risk of phototoxicity similar to that observed with ciprofloxacin. Appropriate information on the phototoxicity potential is reflected in the SmPC and PL.

2.5.4.8. Other toxicity studies

Potential mutagenicity of three possible impurities in the drug substance were evaluated (NC-185, NC- 186, NC-198). No specific concern was identified as these impurities tested negative in a standard battery of tests for mutagenic activity in the *S. typhimurium* strains TA1537, TA98, TA100, and TA1535 and in the *E. coli* strain WP2 *uvrA*, with and without metabolic activation.

A 2-week repeat-dose hepatotoxicity screen in rats was conducted with rezafungin (2, 6, or 20 mg/kg/day IV) and compared with anidulafungin (40 mg/kg/day IV) as a positive control; this study demonstrated no liver histopathology with rezafungin but elevations in serum transaminase and hepatocellular single-cell necrosis with anidulafungin.

A study evaluating different modes of IV administration (slow bolus, 20- or 60- minute IV infusion) into a tail vein of rats was conducted and the results supported slow bolus dosing for the pivotal GLP 4-week rat toxicity study. In addition, an investigative study to evaluate histamine plasma levels in rats after a single IV slow bolus dose was also conducted; this study demonstrated acute dose- related increase in plasma histamine levels along with associated signs of histamine release (swollen facial area, hypoactivity, impaired equilibrium, and/or blue extremities).

In the single dose non-GLP SC study in monkeys, no adverse local SC effects were observed at 30 mg/kg (highest dose tested). In the multiple dose SC study, no adverse local effects were observed after the first dose of 30 mg/kg, but adverse effects were seen after multiple doses when administered via SC route at high concentrations every 3 days for 2 weeks.

Rezafungin was also tested in an *in vitro* functional mitochondrial cellular toxicity assay up to free-drug concentrations of 21 µM and found to have no effect on extracellular oxygen levels and pH indicating rezafungin has no effects on mitochondrial oxidative phosphorylation and glycolysis.

Overall, the potential worst case exposure levels of all the extractable/leachable materials from IV bags and manufacturing contact parts in contact with rezafungin show no clear cause for concern for human safety, based on the most conservative permitted daily exposure. Additionally, the extractables detected from the IV-based rezafungin drug delivery systems and manufacturing contact parts also show no clear cause for concern for human safety based on available data.

2.5.5. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) provided by the Applicant is in accordance with the *Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00, June 2006) and the *Questions and Answers on 'Guideline on the environmental risk assessment of medicinal products for human use'* document (EMA/CHMP/SWP/44609/2010 Rev. 1, 2016).

An ERA Phase I was conducted to consider the risk to the environment arising from the use of Rezafungin indicated for the treatment of adult patients with invasive candidiasis. Relevant endpoints, methods used and results obtained were discussed and study results are summarised in the following Table 1.

Table 1. Summary of main study results

Substance (INN/Invented Name): REZAFUNGIN ACETATE			
CAS-number (if available): 643573			
PBT screening		**Result**	**Conclusion**

Bioaccumulation potential- log Kow	OECD107	0.78, 1.47 and 0.84 at pH 5, 7 and 9, respectively	Potential PBT **N**
PBT-statement:	The compound is not considered as PBT		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default and refined	Default: 0.2 Refined: 0.00074	µg/L	> 0.01 threshold **N**
Other concerns (e.g. chemical class)			**N**

Log Dow values experimentally determined at environmentally relevant pH values (5, 7 and 9) were 0.78, 1.47 and 0.84, respectively, far below the trigger value of 4.5. Therefore, Rezafungin is not a persistent and bioaccumulative substance, and no further screening of persistence, bioaccumulation, and toxicity (PBT) assessment is required.

Refined PECsurfacewater (PECsw) based on the prevalence of candidemia, and the treatment regime is according to the document Questions and answers on *Guideline on the environmental risk assessment of medicinal products for human use*" document (EMA/CHMP/SWP/44609/2010 Rev. 1, 2016). The refined PECsw value is below the action limit defined by EMA which indicates that a Phase II, environmental fate and effects is not required.

Precautionary and safety measures taken to reduce the risk to the environment, and enhance environmental protection, on the SmPC were applied by the applicant, according to "*Guideline on the environmental risk assessment of medicinal products for human use*" (EMEA/CHMP/SWP/4447/00 corr 2, 2006).

Conclusions on ERA:

An environmental risk assessment has been performed according to the relevant guidelines, to evaluate the potential environmental risk resulting from the use of Rezafungin 200 mg powder for concentrate for solution for infusion. Considering the above data, Rezafungin 200 mg powder for concentrate for solution for infusion does not significantly increase rezafungin concentration in the environment and is not expected to pose a risk to the environment when used as prescribed.

2.5.6. Discussion on non-clinical aspects

Single dose toxicity studies in rats revealed effects attributed to an acute histamine release response. Section 5.3 of the proposed SmPC adequately refers to this acute histamine-release response in rats.

Pivotal repeated dose toxicity studies include studies in rats and cynomolgus monkeys with treatment durations, in both animal species, of 4, 13 and 26 weeks.

Effects on male reproductive organs and spermatogenesis were observed in repeated dose toxicity and male fertility studies in rats when the dose was administered once every 3 days. No such effects were observed in monkeys. Effects on male reproductive organs were not observed in the chronic toxicity studies, with administration once a week, conducted in rats and sexually mature cynomolgus monkeys.

According to the Applicant, the findings observed in the male fertility and 13-week repeated dose toxicity studies in rats were considered to be consistent with an injury to Sertoli cells, likely to be an effect similar to another echinocandin (micafungin) and not relevant to humans. Nevertheless, since the human relevance is not fully clear, information on effects on male reproductive organs and spermatogenesis observed in rats has been adequately included in the SmPC (sections 5.3 and 4.6).

The vehicles used in the pivotal studies in rats and monkeys differed in terms of the concentration of tween 80 – 2.5% in studies in rats and 1.25 or 0,5% in studies in monkeys. The same generally applied to the non-pivotal repeated dose toxicity studies. The clinical formulation once reconstituted is 4.5% Polysorbate 80 at 20 mg/ml, this is further diluted prior to administration in 250 mL, according to SmPC, and therefore final % tween for 1 vial = 1.8 mg/ml (0.18%) and for 2 vial loading dose = 3.6 mg/ml (0.36%). This is lower than the % used in the nonclinical studies.

The differences in concentrations of Polysorbate 80 (PS80) in formulations used in nonclinical studies versus the clinical formulation were explained by the Applicant, as being related to the need to maximise systemic exposures in animals, as PS80 is included as a solubiliser of rezafungin acetate. It was however, also noted that differences in concentrations of PS80/ rezafungin solubility may have an impact on injection site reactions. Also taking into account that there is clinical experience with the clinical formulation, no further clarifications were considered needed.

The Applicant has discussed the Schwann cell inclusions, observed in studies conducted in rats and cynomolgus monkeys, in terms both of its causes and human relevance. According to the provided discussion, the inclusions are interpreted as phospholipidosis (PLD). The development of PLD after treatment of rezafungin is thought to be likely associated with the compound's cationic amphiphilic properties, as PLD is known to be caused by long-term treatment with other cationic amphiphilic drugs. The precise molecular process behind PLD has yet to be fully elucidated.

The Applicant claimed that the finding of Schwann cell inclusions is not relevant to humans since there were no associated degenerative, inflammatory, or other lesions associated with the Schwann cell inclusions. PLD was not associated with axonal degeneration, axonopathy or biologically significant changes in nerve conductance velocity. In the 6-month monkey study neuro-electrophysiological evaluations demonstrated that sensory and motor nerve conduction remained within functional physiological ranges at all timepoints (Week 13 and 25) and in the 6-month rat study there were no test article-related effects on functional observation battery parameters. Therefore, and taking into account the SmPC guideline, the Applicant also considered it unnecessary to include any statements relating to PLD in the SmPC, which was agreed by the Committee.

Available data suggested that rezafungin could induce tremors in cynomolgus monkeys with unclear human relevance. The Applicant was therefore asked to provide further clarifications in this respect.

The Applicant explained that the 6-month study was not the first study in cynomolgus monkeys where tremors were observed in the animals from control group. In an early exploratory and tolerability study conducted with rezafungin, individual control animals showed some degree of mild generalised tremor. Additionally, the Applicant noted that the same test facility was used for all pivotal toxicology studies including the rezafungin chronic monkey toxicology study and that it could be excluded the possibility of a contamination of the control formulation used in the 6-month study in cynomolgus monkeys. No test article was detected in the vehicle administered to the control group and no rezafungin was detected in plasma samples taken from control monkeys in the 6-month study. Results from retrospective analysis to determine the prevalence of incidental clinical observations which could be interpreted as neurologically related in

control animals revealed that tremors were amongst the most frequently observed neurological clinical signs at the test facility.

Regarding possible mechanism, the Applicant provided separate discussions for generalised versus intentions tremors:

Generalised tremors

Both the 6-month and a supporting non-GLP 1-month tolerability and toxicokinetic study in cynomolgus monkeys employed a blinded examination to prevent any potential bias. In the 1-month study, animals were dosed rezafungin at 0 or 30 mg/kg/dose; in the 6-month, 0, 5, 15 or 30 mg/kg/dose. According to information provided by the Applicant, in the non-GLP study, all clinical observations in the test article-treated group were noted with similar incidence in the control group, were limited to single animals, and/or were considered common findings for laboratory monkeys of that age and breed. In the 6-month study, the only neurological findings noted with any degree of consistency during the dosing procedure or at the cage side observation period were generalised slight tremors. There were no differences between control and treated groups in the numbers of animals displaying generalised tremors, in the number of occurrences and in their severity.

The observed generalized tremors were considered to be likely related to general background stress.

Intention tremors

Intention tremors were only observed in the first 3-month monkey study with rezafungin administration every 3 days (NC-118) and most frequently at 60/45 mg/kg (margin of exposure based on AUC0-168 at the end of dosing ≥15-fold). In the studies that followed (NC-184 and NC-190), which employed once weekly dose administration up to 30 mg/kg intention tremors were not observed.

The cause of intention tremors was considered to be unknown. The observation on intentions tremor in NC-118 could be an indication that very high doses of rezafungin are able to achieve sufficient central nervous system (CNS) penetration to cause unwanted, but reversible, CNS effects.

Considering that the available information suggests that rezafungin may induce dose-dependent intention tremors with relatively low safety margins (2.53 to 6.15- fold, based on systemic exposure [AUC0-168] from the 13-week [NOAEL of 10 mg/kg/dose, since intention tremors were observed at ≥30 mg/kg/dose] and 6 months study [NOAEL of 30 mg/kg/dose, the maximum tested dose]) and also taking into account results from the secondary pharmacodynamics studies - rezafungin inhibited mean radioligand binding >50% of a number of CNS-related targets – information on intention tremors has been included in section 5.3 of the SmPC. This information is the following: "*Reversible intention tremors (defined as a tremor that is more pronounced when movements are initiated) were observed in one 3-month monkey study with administration once every 3 days and had higher incidence at ≥ 30 mg/kg. The no observed effect level (NOEL) for intention tremors is considered to be 10 mg/kg in this study (about 2.5 times the clinical dose based on AUC comparisons). Intention tremors were not observed in the 6-month monkey study, in which animals were dosed intravenously once a week with up to 30 mg/kg (about 5.8 times the clinical dose based on AUC comparisons) or in any rat studies*".

The information included on intention tremors in section 5.3 of the SmPC is adequate.

Reproductive toxicity studies comprised studies on fertility and early embryonic development (Sprague Dawley rats), embryo-fetal development (Sprague Dawley rats, New Zealand White rabbits) and pre and postnatal development (Sprague Dawley rats). No studies in juvenile animals have been conducted. The lack

of such studies is accepted, as the present Marketing Application Authorization refers to the use of Rezzayo in adult patients only.

Consistently with the results from the repeated dose toxicity studies, the studies on fertility and early embryonic development showed effects in testes, epididymides and spermatogenesis. As mentioned before, information on the effects observed on male rat reproductive organs and spermatogenesis has been adequately included in the SmPC.

ERA

Phase I was performed to estimate the exposure to the environment. Log Dow values experimentally determined at environmentally relevant pH values (5, 7 and 9) were < 1.47, far below the trigger value of 4.5. Therefore, Rezafungin is not a persistent and bioaccumulative substance, and no further screening of persistence, bioaccumulation and toxicity (PBT) assessment is required.

Since the Refined PECsurface water is below the action limit of 0.01μg/L, the absence of a Phase 2 ERA is justified, according to "*Guideline on the environmental risk assessment of medicinal products for human use*" (EMEA/CHMP/SWP/4447/00 corr 2, 2006).

In addition, no carcinogenic, mutagenic and/or reproduction effects were reported in the published scientific studies on Rezafungin toxicity. Furthermore, no potential for endocrine disruption was reported as well.

Considering the information mentioned in this report and the proposed precautions related to the use and disposal of this medicinal product, it could be concluded Rezafungin 200 mg powder for concentrate for solution for infusion can be marketed without presenting relevant risks for the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the non-clinical package provided by the applicant provides adequate evidence supporting the clinical use of rezafungin in the applied therapeutic indication, and the SmPC in general reflects the findings.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

Rezafungin is administered IV, and as such the dose is 100 % bioavailable. Therefore, biopharmaceutic studies are not applicable. As only one dosage form and strength are proposed, issues of dose- or strength-proportionality do not arise.

Distribution

Using ultracentrifugation (NC-121 and NC-137), the range of protein binding values were 96.4% to 98.0% (mean or median = 97.4%) in human plasma. The corresponding mean (or median) % free-drug value was 2.6% in human plasma.

For doses of 50 to 400 mg the mean volume of distribution at steady state (Vss) and mean apparent volume of distribution during the terminal phase (Vz) ranged from 33 to 48 L. These data indicate that rezafungin has a volume of distribution approximately equal to body water. This supports the body-wide tissue distribution required for treatment of IC.

Elimination

Following single IV doses of rezafungin over the dose range 50 – 400 mg mean total body clearance was low (range 3.5 – 3.8 mL/min) and the mean apparent terminal half-life ranged from 127-146 hours, consistent with a once weekly dosing regimen.

In single and multiple ascending dose Phase 1 studies, the fraction of rezafungin dose excreted in urine as unchanged rezafungin was <1% at all dose levels, indicating negligible contribution of renal clearance in rezafungin excretion (CD101.IV.1.01 and CD101.IV.1.02).

In a Phase 1 study where healthy subjects were dosed [14C] rezafungin, based on interpolated data (using data from the subjects' return visits to the clinical research unit [CRU] on Days 29 and 60), it was estimated that the majority of the dose (an overall mean estimate of 88.3%) would have been recovered had the subjects been continuously confined to the clinic through Day 60. Of the recovered radioactivity, approximately 74% was recovered in faeces, and 26% was recovered in urine, indicating that elimination of rezafungin is predominantly faecal excretion. Radiochemical analysis indicated that radioactivity in urine was primarily due to metabolites, whereas radioactivity in faeces was primarily rezafungin.

In vitro, rezafungin was stable when incubated with hepatocytes from rats, dogs, cynomolgus monkeys, and humans (NC-010). In incubations with liver and intestinal microsomes from rats, dogs (intestinal only), cynomolgus monkeys and humans, rezafungin was metabolically stable (NC-011, NC-048). A further investigation involving incubation of rezafungin with liver microsomes from mice, rats, cynomolgus monkeys, and humans showed that no metabolites were generated by the end of incubations (Study NC-014). Rezafungin when incubated in phosphate buffered saline is chemically stable, with no evidence of formation of reactive intermediates.

Metabolite identification was performed on plasma, urine and faeces obtained from a Phase 1 study to evaluate the excretion, metabolism, PK, and mass balance following a single IV dose of [14C] rezafungin (~400 mg/200 µCurie [µCi] of radioactivity) in nine healthy adult male subjects (CD101.IV.1.12). Analyses by HPLC and LC-MS/MS of plasma, urine, and faecal samples indicated that rezafungin underwent minimal metabolism in human subjects to produce 14 metabolites, of which 13 were identified and characterised. In plasma, metabolites were present at low levels relative to parent. Rezafungin was the most abundant circulating component, accounting for ~77% of total radiocarbon AUC. Hydroxyrezafungin metabolites

M1241_1, M1241_2, and M1241_3 were the most abundant circulating metabolites. Each individual metabolite accounted for less than 10% of the total plasma radioactivity exposure.

Radiochemical analysis indicated that radioactivity in urine (a minor elimination pathway accounting for ~26% of the recovered radioactivity) was primarily due to metabolites hydroxylated (in one of three positions) or dealkylated (resulting in des-pentyl), whereas radioactivity in faeces (~74% of the recovered radioactivity) was primarily rezafungin. No discussion was provided on how the elimination via faeces occurs.

Dose proportionality and time dependencies

Single and multiple dose PK parameters of rezafungin have been determined in healthy subjects with approximately dose proportional increases in exposure (AUC) over single dose range of 50 mg to 1400 mg and multiple dose range of 100 to 400 mg. These data indicate that rezafungin exhibits linear kinetics over a range of single (50 – 1400 mg) and multiple doses (100 – 400mg).

Special populations

A population PK analysis including data from Phase 1, Phase 2 and Phase 3 studies, showed that measures of renal function, serum creatinine and creatinine clearance, were not significant covariates of rezafungin PK. No dose adjustment is required for patients with renal impairment, which is reflected in the SmPC.

The PK of rezafungin (400 mg) was assessed in subjects with moderate (Child-Pugh B, n=8) and severe (Child-Pugh C, n=8) hepatic impairment. Mean rezafungin exposure (AUC) was reduced by approximately 30% in subjects with moderate and severe hepatic impairment compared to matched subjects with normal hepatic function. No dose adjustment is required for patients with hepatic impairment, which is reflected in the SmPC.

A population PK analysis including data from Phase 1, Phase 2 and Phase 3 studies, showed that sex was not a significant covariate of rezafungin PK.

A population PK analysis including data from Phase 1, Phase 2, and Phase 3 studies, showed that race was not a significant covariate of rezafungin PK.

A population PK analysis including data from Phase 1, Phase 2 and Phase 3 studies, showed that BSA was a significant covariate of rezafungin PK. Differences in exposure (AUC0-168h) across the BSA range were not considered clinically meaningful. No dose adjustment is required based on patients' weight, which is reflected in the SmPC.

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. No dose adjustment is required in elderly patients aged 65 years or more, which is reflected in the SmPC.

Rezafungin has not been studied in paediatrics.

Pharmacokinetic interaction studies

The possible effect of rezafungin on inhibition or induction of drug metabolising enzymes, or inhibition of drug transporters has been ruled out with a combination of in vitro and in vivo studies. Therefore, the need for

dose adjustments is considered unlikely for drugs that are substrates for the range of cytochrome P450 enzymes and drug transporter proteins assessed, when administered with rezafungin. Furthermore, no dose adjustments are necessary for tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax when administered with rezafungin.

Pharmacokinetics using human biomaterials

A study (NC-013) to investigate the effects of rezafungin on CYP 2C8 and CYP 3A4 determined that rezafungin was a weak inhibitor (IC50>25 μM) of both isoforms. A further investigation (NC-153) confirmed that rezafungin (study concentrations from 0.1 to 25 uM) generated reversible IC50 values of >25 μM against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Rezafungin was also found to not be a time-dependent inhibitor of these major human CYP isoforms when tested up to its solubility limit of 25 μM (NC-153).

There was no evidence of induction (<2-fold increase in mRNA expression) of CYP1A2, CYP2B6, and in the case of CYP3A4 in 2 of 3 donors.

Rezafungin was found not to be a substrate for the following transporters: MDR1 (P-gp), BCRP, and MRP2 (ABC) transporters or the human solute carrier (SLC) transporters, OATP1B1, OATP1B3, OCT1, OCTN1, or OCTN2. Rezafungin was found to be an inhibitor of probe substrate transport mediated via P-gp, OATP1B1, OATP1B3, OAT1, OCT2, OCT1, MATE1 and MATE2-K, but not via BCRP, OAT3 or BSEP.

2.6.2.2. Pharmacodynamics

Mechanism of action

The mechanism of action of echinocandins is widely studied and a more thorough assessment on this subject was performed in the non-clinical development and is described thoroughly in the non-clinical report and overview.

The cell walls of most fungi consist mainly of 1,3-β-D-glucans (at least 50% of the cell wall) which is needed for structural integrity (Hasim and Coleman 2019; Garcia-Effron, Park, and Perlin 2011; Perlin 2011). 1,3-β-glucan is synthesised by 1,3-β-glucan synthase complex, made up of a catalytic domain (Fks) and a regulatory subunit (Rho1). FKS gene disruptions lead to mutants with cell wall defects leading to reduced echinocandin susceptibility. The level of echinocandin resistance seems to be dictated by the particular mutation present (Pham et al. 2014) and three homologous genes (FKS1, FKS2 and FKS3) have been identified so far.

Inhibition studies with rezafungin against wild-type (WT) and fks mutant glucan synthase enzymes from 3 *C. albicans* and 4 *C. glabrata* (NC-038) demonstrated that rezafungin shared the same mechanism of action as other drugs in the echinocandin class as expected. The IC50 values for rezafungin and micafungin against the glucan synthase from the WT *C. albicans* strain were 14.25 and 17.65 ng/mL, respectively (Table 1). Against the glucan synthase from the fks mutants *C. albicans* DPL18 (F641S) and DPL20 (S645P), the IC50 values were 24.3-fold and 185.3-fold higher, respectively, for rezafungin and 100-fold and 144-fold higher, respectively, for micafungin.

Against WT *C. glabrata* DPL1021 glucan synthase, the IC50 values for both drugs were higher compared to those obtained against the WT *C. albicans* enzyme (Table 1) but against the enzyme from the second WT C. glabrata strain, DPL50, rezafungin and micafungin IC50 values were 2.6 and 0.45 ng/mL, respectively (Table

1 and Figure 2). When tested against the glucan synthase form DPL23 (F659del) and DPL30 (S663P) *C. glabrata* mutants, rezafungin lacked activity (IC50 >10,000 ng/mL) and micafungin had IC50 values of >10,000 and 6772 ng/mL, respectively.

From these data, it was concluded that rezafungin is a potent inhibitor of glucan synthesis in WT strains of *C. albicans* and *C. glabrata* and confirms that rezafungin's target is 1,3-β-D- glucan synthase consistent with other members of the echinocandin class.

Primary and secondary pharmacology

Primary PD studies have been conducted by the applicant to investigate the efficacy of rezafungin in *in vitro* and animal models of infection.

In vivo models of infection

Rezafungin has been assessed for *in vivo* efficacy in a broad range of treatment and prophylactic mouse models of candidemia and candidiasis, and invasive aspergillosis. These studies demonstrated the following:

- In single- and multi-dose treatment studies, rezafungin demonstrated significant dose-dependent antifungal efficacy against *C. albicans* and *A. fumigatus*.
- In several studies, rezafungin delivered dose-dependent efficacy in mice when given as a single dose on the day of infection with significant reductions in kidney burdens, relative to vehicle controls, seen up to 168 hrs (NC-044) or 192 hr (NC-097) post- infection at doses as low as 1 mg/kg. Against *Candida auris*, rezafungin demonstrated statistically significantly higher percent survival compared with mice treated with other antifungal drugs or with untreated mice, and significantly lower log10 colony-forming units (CFU) in kidneys compared to those in other groups.
- Rezafungin was efficacious in a mouse model of invasive candidiasis against *C. auris* (NC-150) and demonstrated superior efficacy in kidney fungal burden reduction in a mouse time-kill study of infection with *C. auris*.
- In prophylactic mouse models of candidiasis against *C. albicans*, aspergillosis against *A. fumigatus*, and pulmonary aspergillosis against *A. fumigatus*, rezafungin was found to be efficacious even at low doses. Efficacy increased when the time between treatment and infection was shortened and with increasing rezafungin doses.
- Rezafungin was also found to be efficacious in *Pneumocystis* pneumonia mouse models with efficacy increasing as the time between treatment and infection was shortened and when the dose of rezafungin was increased.
- Dosing of rezafungin either once daily or once per week in a guinea pig model of dermatophytosis against Trichophyton mentagrophytes showed efficacy against this organism compared with the vehicle-treated controls.

Activity in mutant strains

Inhibition studies with rezafungin against wild-type (WT) and fks mutant glucan synthase enzymes from *C. albicans* and *C. glabrata* confirmed that rezafungin's target was 1,3-β-Dglucan synthase, consistent with other members of the echinocandin class. *In vitro* studies and evaluation of resistant surveillance isolates demonstrated that resistance to rezafungin, as with the other echinocandins, can occur via target

modification, and the propensity for resistance to occur is comparatively more common with *C. glabrata* relative to other *Candida* spp. Development of resistance to rezafungin during *in vitro* spontaneous mutation frequency and serial passage assays was low and consistent with that observed for comparator echinocandins. Time-kill kinetic analysis showed sustained killing with rezafungin at multiples of the MIC consistent with that observed with comparator echinocandins, and this killing was also observed with some fks mutant isolates. Comparatively less killing was observed for rezafungin against *C. auris*, in particular for S. African and S. American/Israel clades, compared to other *Candida* species. This, however, is consistent with all echinocandins and was not unique to rezafungin.

The *in vitro* activity of rezafungin has been profiled throughout development against a large number of clinical yeast and mould isolates using CLSI guidelines (CLSI M27, 2017; CLSI M38, 2017). These studies were conducted prior to the availability of a EUCAST-approved standard broth microdilution susceptibility testing method. Studies conducted using CLSI guidelines demonstrated that the activity of rezafungin was consistent with that observed for other currently utilised echinocandins, in particular anidulafungin from which it was derived. Surveillance studies performed annually since 2014 show a consistent activity profile for rezafungin with little to no variation in rezafungin activity observed either by year or geographic region, and low MIC/MEC50/90 values against most isolates of *Candida* spp. and *Aspergillus* spp., characteristic of the echinocandin class.

Rezafungin activity against azole- and echinocandin-resistant isolates was consistent with that observed for other echinocandins. MIC values for rezafungin were elevated for caspofungin non-susceptible isolates relative to caspofungin-susceptible isolates, as seen with all echinocandins. There was, as expected, little to no impact of fluconazole resistance on the activity of rezafungin. Rezafungin also shows activity against biofilms of *Pneumocystis carinii* and *C. albicans*, both in the prevention biofilm formation and disruption of established biofilms. The antimicrobial interaction studies of rezafungin in combination with other currently marketed antifungal and antibacterial agents showed largely additive or indifferent effect, although some synergy was seen between rezafungin and posaconazole against some of the evaluated yeasts and moulds. Overall, these data suggest that rezafungin has a low potential to adversely impact other anti-infective drugs and in turn, if given in combination with other agents, would not be negatively impacted. Rezafungin susceptibility testing using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) EUCAST method for susceptibility testing of yeasts (E.Def 7.3.2) revealed unacceptable inter-laboratory variation among rezafungin MICs, particularly against *C. albicans*.

Table 27. Summary of rezafungin and comparator echinocandin activity against commonly encountered *Candida* species (CLSI)

Organism	Rezafungin		Caspofungin			Anidulafungin			Micafungin		
	n	$MIC_{50/90}$ (mg/L)	n	$MIC_{50/90}$ (mg/L)	%R	n	$MIC_{50/90}$ (mg/L)	%R	n	$MIC_{50/90}$ (mg/L)	%R
C. albicans	2371	0.03/0.06	2350	0.016/0.12	0.3	2351	0.016/0.06	0.1	2246	0.016/0.03	0.3
C. glabrata	1131	0.06/0.12	1111	0.03/0.5	14.9	1111	0.06/0.12	3.2	1006	0.016/0.03	3.0
C. tropicalis	672	0.03/0.06	653	0.03/0.25	2.3	653	0.016/0.06	0.6	551	0.03/0.06	1.1
C. parapsilosis	946	1/2	930	0.25/1	0.0	927	2/2	0.1	835	1/2	0.0
C. krusei	335	0.03/0.12	320	0.25/1	11.6	320	0.03/0.12	0.3	216	0.12/0.25	0.9
C. dubliniensis	180	0.06/0.12	180	0.03/0.12	-	180	0.03/0.12	-	180	0.03/0.03	-
C. auris	19	0.06/0.12	19	0.5/1	-	19	0.06/0.25	-	19	0.25/0.5	-
	100	0.12/0.5	-	-	-	-	-	-	-	-	-
	38	0.25/16	38	0.5/4	10.5	-	-	-	38	0.12/16	10.5
C. rogusa	54	0.5/1	-	-	-	-	-	-	-	-	-
C. kefyr	52	0.06/0.12	52	0.25/0.5	-	52	0.03/0.06	-	52	0.06/0.12	-
C. lusitaniae	46	0.12/0.25	46	0.5/1	-	46	0.03/0.06	-	46	0.12/0.25	-
C. inconspicua	41	0.06/0.06	41	0.25/0.5	-	41	0.008/0.016	-	41	0.03/0.06	-

MIC = minimum inhibitory concentration; MIC_{50} = MIC against 50% of the isolates; MIC_{90} = MIC against 90% of the isolates; %R = percent resistant based on CLSI interpretive criteria ("M60Ed2 | Performance Standards for Antifungal Susceptibility Testing of Yeasts, 2nd Edition" n.d., 60)
Source: NC-031, NC-039, NC-064, NC-073, NC-074, NC-110, NC-138, NC-142, NC-144, NC-149, NC-163, NC-188, NC-194, NC-195, NC-213, NC-214; Data on file.

In vivo studies conducted with rezafungin against fks mutant strains of *C. albicans* demonstrated limited efficacy against an FKS/fks mutant strain and no efficacy against an fks/fks *C. albicans* strain consistent with that seen with other echinocandins. However, rezafungin was effective against an azole-resistant isolate of *C. albicans* and against an azole-resistant *A. fumigatus* isolate where lung and kidney fungal burdens were reduced, and survival was substantially improved.

Mechanism of echinocandin resistance

The echinocandin resistance mechanism among *Candida* spp. has been well characterized and involves mutations in "hot spot" regions of FKS genes encoding the enzymatic target glucan synthase. Modification within these regions at residues Phe641 – Pro649 and Arg1361 (*C. albicans* locations) and homologous regions of Fks2 in *C. glabrata* have been linked to reduced echinocandin activity (Perlin 2015a; Kurtz et al. 1996). Of note, FKS1 mutations have also been linked to echinocandin resistance within the emerging pathogen *C. auris*. Rezafungin mutants selected in vitro had mutations within these regions as expected.

Development of resistance studies with rezafungin:

- Overall, the potential for resistance development to rezafungin in vitro as assessed during spontaneous mutation frequency and serial passage assays was low and was consistent with the echinocandin comparators.
- The frequency of spontaneous, single-step mutations that led to decreased susceptibility to rezafungin in the tested *Candida* spp. ranged from 1.35 x 10-8 to 3.86 x 10-9 for the evaluated *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. krusei*.
- Most of the mutants isolated from *C. albicans*, *C. parapsilosis* and *C. krusei* had ≤2-fold MIC increases compared to the wild-type parent strains, whereas the C. glabrata mutants isolated were observed to have higher MIC fold-shifts from the parent MIC values, presumably due to the haploid nature of its

FKS genes.

- Rezafungin mutants that demonstrated a ≥4-fold MIC shift against the selecting drug also displayed cross-resistance to one or more of the tested echinocandins.
- Similar results were observed during serial passage; the largest increases in MIC values during passage was observed with *C. glabrata* with comparatively little change in MIC during passage of *C. parapsilosis* and *C. krusei*.
- During serial passage of *C. albicans*, no fks mutants were selected with rezafungin but an 8-fold increase in MIC was observed at Passage 15 and Passage 20.

In contrast, an fks mutant was selected with anidulafungin with a corresponding 64-fold increase in MIC at Passage 20. In conclusion, although resistance to echinocandins is not commonly encountered during surveillance, *in vitro* studies and evaluation of resistant surveillance isolates demonstrate that resistance to rezafungin and the comparator echinocandins can occur via target modification, and the propensity for resistance to occur is comparatively more common with *C. glabrata* relative to other *Candida* spp. Development of resistance to rezafungin during *in vitro* spontaneous mutation frequency and serial passage assays was consistent with that of other echinocandins.

Reduced susceptibility to echinocandins arises from mutations in glucan synthase catalytic subunit-encoding FKS genes (FKS1 for most *Candida* spp.; FKS1 and FKS2 for *C. glabrata*) that impact residues comprising "hotspot" (HS) regions of the Fks protein. The frequency of single-step spontaneous mutations conferring some level of reduced susceptibility to rezafungin in *C. albicans*, *C. glabrata*, *C. krusei*, and *C. parapsilosis* were low and comparable to other echinocandins at 1× MIC, ranging between 10-8 and 10-9. Serial passage of these same strains on antifungal drug gradient plates also demonstrated a low potential for resistance development with rezafungin passage #20 MIC values all ≤1 µg/mL (4 µg/mL for *C. parapsilosis*). Rezafungin exhibits some degree of cross-resistance to all fks mutations that confer reduced susceptibility to echinocandins.

Effects of rezafungin on QT Interval and Other ECG Intervals

The effect of rezafungin on the QT interval and other ECG intervals was assessed in healthy adult subjects (Study CD101.IV.1.06). The doses of rezafungin administered were 600 mg and 1400 mg and were selected to achieve relevant therapeutic and supratherapeutic exposures, respectively.

The effect of rezafungin on the QT interval and other ECG intervals was assessed in a Phase 1, single-centre, randomised, comparative study of the effect of single-ascending doses of rezafungin (n = 12 at each dose level), a negative control (placebo; n = 12), and a positive control (moxifloxacin 400 mg plus IV placebo; n = 24) in healthy adult subjects. Of particular focus was the effect on the QT interval corrected for heart rate by Fridericia's formula (QTcF). A total of 60 subjects were enrolled and completed all treatments assigned.

The primary PD ECG outcome measure was the following:

- Assess the effects of Rezafungin for Injection versus IV placebo on the QT interval of the electrocardiogram (ECG) corrected for heart rate by Fridericia's formula (QTcF) in healthy adult subjects.

Secondary PD ECG outcome measures and analyses for subjects in the rezafungin and IV placebo dose groups were the following:

- Determine the difference, if any, in the effect between Rezafungin for Injection and IV placebo on the QTcF interval between male and female subjects.

- Evaluate differences in the effects of Rezafungin for Injection and IV placebo on the proportion of subjects with QTcF and changes of QTcF from baseline exceeding specified values, and interval data

and changes from baseline in other ECG intervals (HR, PR interval, QRS duration); and on emergence of diagnostic findings (with a focus on abnormal ST segment, T wave, or U wave morphologies).

- Evaluate the PK profile of Rezafungin for Injection.

- Assess the safety and tolerability of Rezafungin for Injection.

Table 2: Summary of Study Design

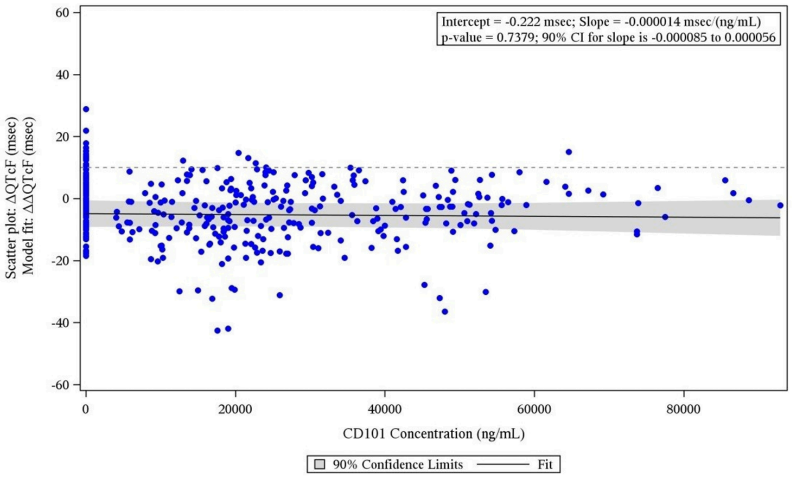
	Treatment	Rezafungin for Injection	IV Placebo	Oral Moxifloxacin
Cohort 1	Dose Groups	Single dose (600 mg) in a 375 mL infusion over 1.5 h (± 5 min) followed by IV placebo in a 500 mL infusion over 2 h (± 5 min)	IV Placebo in a 375 mL infusion over 1.5 h (± 5 min) followed by IV placebo in a 500 mL infusion over 2 h (± 5 min)	Single dose (400 mg) administered with approximately 240 mL of water plus IV placebo in a 375 mL infusion over 1.5 h (± 5 min) followed by IV placebo in a 500 mL infusion over 2 h (± 5 min)
	Number of Subjects[a]	12	6	12
Cohort 2	Dose Groups	Single dose (1400 mg) divided into a 375 mL infusion over 1.5 h (± 5 min) followed by a 500 mL infusion over 2 h (± 5 min)	IV Placebo in a 375 mL infusion over 1.5 h (± 5 min) followed by IV placebo in a 500 mL infusion over 2 h (± 5 minutes)	Single dose (400 mg) administered with approximately 240 mL of water plus IV placebo in a 375 mL infusion over 1.5 h (± 5 min) followed by IV placebo in a 500 mL infusion over 2 h (± 5 min)
	Number of Subjects[a]	12	6	12
Total Number of Subjects		24	12	24

IV = intravenous
[a]Subjects were randomized 2:1:2 for the Rezafungin for Injection, IV placebo, and oral moxifloxacin groups.

The primary endpoint was based on an analysis of the regression of ΔQTcF as a function of rezafungin plasma concentration to derive the estimated mean ΔΔQTcF for the rezafungin dose groups at the geometric mean Cmax for each dose level. The outcome was defined by a comparison of the upper bounds of the 2-sided 90% CIs with 10 msec. A linear model best fit the data with a statistically nonsignificant slope (p = 0.7379), as shown in Figure 1. From this model, the estimated mean ΔΔQTcF at the geometric mean plasma concentrations for the rezafungin doses had upper bounds < 10 msec (Figure 2). The geometric mean Cmax of rezafungin 1400 mg IV, (59,612 ng/mL) the estimated ΔΔQTcF was -5.7 msec with a 2-sided 90% CI upper bound of -1.4 msec. At the geometric mean Cmax of rezafungin 600 mg IV, (27,972 ng/mL) the estimated ΔΔQTcF was -5.3 msec with a 2 sided 90% CI upper bound of -1.5 msec.

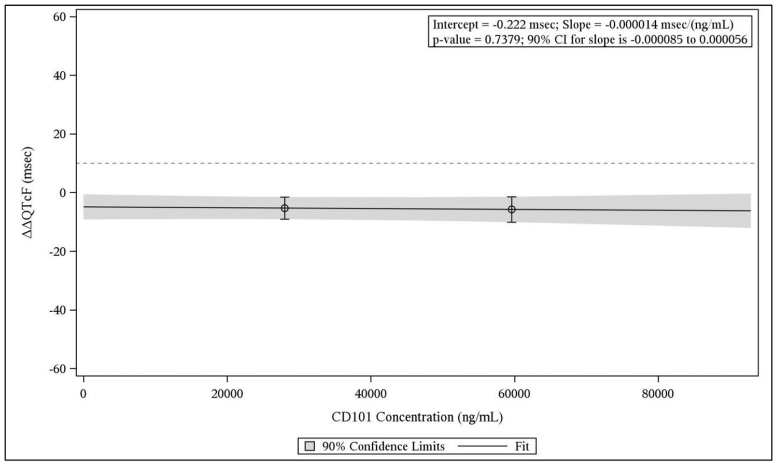
A single subject who received rezafungin 1400 mg, had 4 values of QTcF > 450 msec after a baseline QTcF of 444.7 msec. Specifically, the values were between 450.3 and 459.7 msec. Three timepoints occurred within the first 4 hours post-start of infusion (1.5, 2.5 and 3.5 hours), and the fourth timepoint occurred at 168 hours post-start of infusion. No other subjects had elevated QTcF values and no values of ΔQTcF were > 30 msec for placebo or rezafungin.

Figure 1: **Rezafungin Regression Analysis: Scatter Plot of Change of QTcF from Baseline (ΔQTcF) for Rezafungin and Placebo Subjects versus Rezafungin Concentration; and Linear Model Slope and 2-sided 90% Confidence Bounds of the Slop Representing Placebo-adjusted Change of QTcF from Baseline (ΔΔQTcF) (msec)**



Definition: CD101 = rezafungin
Source: Figure 16, ECG Cardiac Safety Report

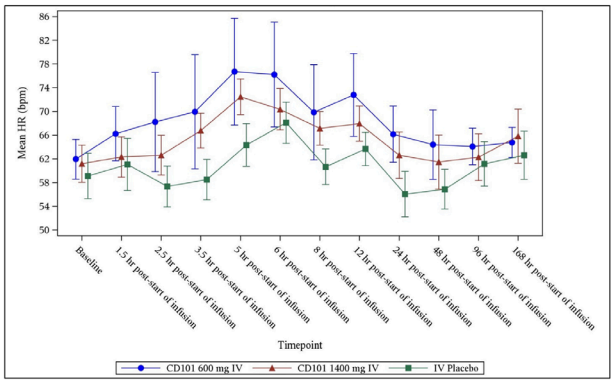
Figure 2: **Rezafungin Regression Analysis: Estimated Placebo-adjusted Mean Change of QTcF from Baseline (ΔΔQTcF) at the Geometric Mean Rezafungin Plasma Concentrations and 2-sided 90% Confidence Bounds (msec)**



Definition: CD101 = rezafungin
Source: Figure 17, ECG Cardiac Safety Report

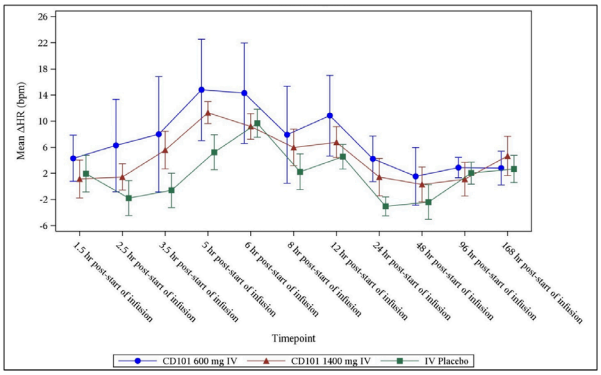
Mean HR findings were unremarkable with slightly higher mean HR values for all rezafungin and placebo subjects from approximately 5 through 12 hours post-start of infusion. Mean changes from baseline reflected these increases, maximally 14.8 bpm at 5 hours and 14.3 bpm at 6 hours post-start of infusion for the rezafungin 600 mg IV group. For the rezafungin 1400 mg IV group, the mean changes from baseline were likewise maximal at those timepoints, with values 11.3 and 9.2 bpm. At the 5-hour timepoint the placebo group had a mean increase of 5.2 bpm and the value at 6 hours was 9.7 bpm.

Figure 5: Mean Heart Rate and 2-sided 90% Confidence Interval (bpm)



Definition: CD101 = rezafungin
Abbreviations: HR = heart rate, bpm = beats per minute, IV = intravenous
Source: Figure 10, ECG Cardiac Safety Report

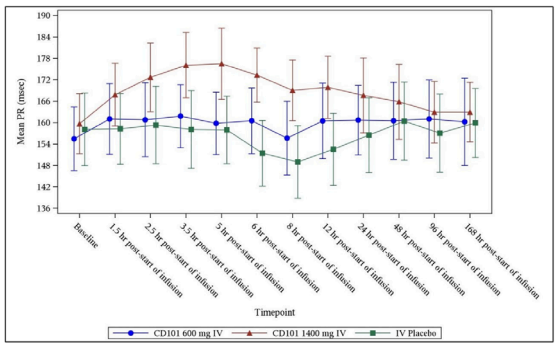
Figure 6: Mean Change from Baseline in Heart Rate and 2-sided 90% Confidence Bounds (bpm)



Definition: CD101 = rezafungin
Abbreviations: HR = heart rate, bpm = beats per minute, IV = intravenous
Source: Figure 11, ECG Cardiac Safety Report

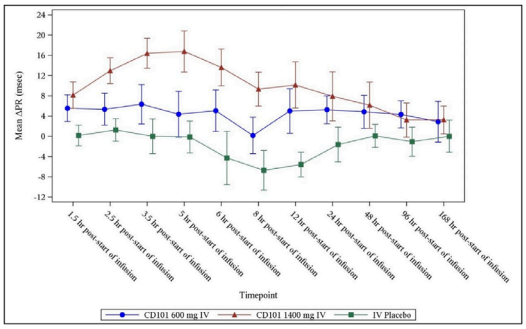
Mean PR interval values were in the normal range but the rezafungin 1400 mg IV group had moderately higher values during the observations from 2.5 to 24 hours post-start of infusion with a maximum mean PR was 176.5 msec at 5 hours. There was little variation in mean PR for the rezafungin 600 mg IV or placebo groups. The mean change from baseline for the rezafungin 1400 mg IV group, maximally 16.8 msec at 5 hours post-start of infusion, were all greater than 7.9 msec from 1.5 hours to 24 hours post-start of infusion. Subjects in the rezafungin 1400 mg IV group had moderate increases in PR compared with the placebo group, the time course of the increases was roughly correlated with plasma concentration levels and increases of ≥ 20 msec were noted in half of the treatment group. Individual values were < 220 msec, and changes of PR from baseline were less than a 25% increase.

Figure 7: Mean PR and 2-sided 90% Confidence Bounds (msec)



Definition: CD101 = rezafungin
Abbreviations: IV = intravenous
Source: Figure 12, ECG Cardiac Safety Report

Figure 8: Mean Change from Baseline in PR and 2-sided 90% Confidence Bounds (msec)



Definition: CD101 = rezafungin
Abbreviations: IV = intravenous
Source: Figure 13, ECG Cardiac Safety Report

Mean QRS values were normal and mean changes from baseline were minimal, ranging from 0.4 to 4.7 msec.

The data shows that therapeutic and supratherapeutic doses of Rezafungin for Injection did not have an adverse effect on the QT interval in healthy subjects.

The primary study objective was met in demonstrating no effect of rezafungin on the QTcF interval. The estimated mean ΔΔQTcF at the geometric mean plasma concentrations for the rezafungin doses had upper bounds of < 10 msec.

Secondary determination of mean ΔΔQTcF at each timepoint by dose showed all 1-sided 95% upper bounds to be < 10 msec.

Secondary objectives also were met for the study. No difference in QTcF interval was seen between male and female subjects who received rezafungin or placebo. Mean HR findings were unremarkable with slightly higher mean HR values for all rezafungin and placebo subjects from approximately 5 through 12 hours post-start of infusion. Mean QRS values were normal and mean changes from baseline were minimal.

The plasma PK of rezafungin was generally well characterized following administration of the 600 mg and 1400 mg doses. Exposure to rezafungin increased in an apparent dose-linear manner with the increase in the rezafungin dose. Geometric mean rezafungin overall (AUCs) and Cmax exposures following a single IV infusion administration of 1400 mg rezafungin were greater than 2.0-fold that of a single IV infusion administration of 600 mg rezafungin.

2.6.3. Discussion on clinical pharmacology

Clinical PK

REZZAYO 200 mg powder for concentrate for solution for infusion is indicated for the treatment of invasive candidiasis in adults. The active pharmaceutical ingredient (API) is rezafungin acetate. This is an article 8(3) application of a new drug entity and a full dossier was submitted.

Regarding the clinical Pharmacokinetic evaluation of the drug, rich data is available from Eight Phase 1 studies with extensive PK sampling have been conducted for rezafungin, including single and multiple-dose pharmacokinetic (PK) studies, drug-drug interaction (DDI) studies, hepatic impairment, and Excretion/Metabolism/PK studies in healthy volunteers. Also, sparce PK sampling data from Phase 2 and Phase 3 safety and efficacy studies for treatment of candidemia and/or invasive candidiasis were included in a population PK analysis.

Fully validated methods, with acceptable performance and similar behaviour in different analytical sites were used in order to quantify the plasma and urine concentrations of rezafungin in the various samples obtained in the clinical trials. In study performance was also assessed and confirmed by ISR in all the studies showing acceptable performance.

A non-compartmental analysis was performed in all the phase 1 clinical studies. A popPK analysis was also developed based upon data from five Phase 1 studies, a Phase 2 study, and a Phase 3 study. The final base model found to best describe the available data was a 3-compartment model with first-order elimination characterised by the PK parameters clearance (CL), central volume of distribution (V1), shared parameter of peripheral volume of distribution for both peripheral compartments (V23), intercompartmental clearance 1 (Q2), and intercompartmental clearance 2 (Q3).

The impact of intrinsic and extrinsic factors on the PK variability of rezafungin was evaluated and albumin concentrations (on V23), body surface area (on CL, V1 and V23), and disease state (on CL and V1) were found to be statistically significant covariates and included in the final population PK model. Disease state was defined as patients from the Phase 2 and Phase 3 studies and hepatically impaired subjects. Other factors assessed including sex, race, age, liver function tests, and estimated creatinine clearance did not explain the variability in the PK of rezafungin.

The final population PK model of rezafungin was a 3-compartment model with first-order elimination, characterised by the parameters CL, V1, V23, Q2 and Q3. The second and third compartment shared the same volume but considered different intercompartmental clearances. The variability model included interindividual variability in CL, V1, and V23 and their covariabilities, and a proportional residual variability model.

Model evaluation demonstrated that this model adequately described the observed plasma concentration data. The final fixed and random effect parameters were determined with good precision. Shrinkage was also low. The GOF plots did not shown any relevant tendency and the presented VPCs (stratified by the first dose) also showed a good description of both the central tendency and variability by the model. The VPCs and pcVPCs of the data from the different clinical studies included in the PopPK model shown no relevant miss specification in the model, with a good agreement between the median and 10th/90th percentiles on both the in vivo and the simulated data. Overall, the model seemed to be well suited for the intended purpose.

Individual rezafungin PK exposure estimates (AUC 0-168h and Cmax), for a 400 mg dose on Day 1, were generated for each subject in the analysis dataset, and used to assess the overall variability in rezafungin exposure across a wide range of patient factors including the statistically significant covariates. Of the statistically significant covariates (BSA, albumin and disease state) the covariate with the largest impact on exposure (AUC0-168h) was disease state where the exposure in infected patients and hepatically impaired subjects was approximately 30% lower than healthy subjects. This difference is also likely to reflect inherent differences in albumin levels as healthy subjects have higher albumin levels compared to infected patients and hepatically impaired subjects. Other patient factors were also explored, including renal function. Of the patients in the Phase 2 and Phase 3 studies that were included in the population PK analysis data set (167 in total) 33, 36 and 14 had mild, moderate and severe renal impairment, respectively. A further eight patients had kidney failure, and 76 patients had normal renal function. Comparison of the exposure (AUC0-168h) in patients with renal impairment (including kidney failure) with patients with normal renal function, identified that the range of the geometric mean ratios was 0.95 to 1.23. Of the other selected patient covariates (e.g., age, weight, BMI, sex, race), the geometric mean and 90% confidence interval (CI) were within 0.6 to 1.6 for all comparisons.

- Absorption

Rezafungin is administered IV, and as such the dose is 100 % bioavailable. Only one dosage form and strength are proposed. As such, no issues of dose- or strength-proportionality exist. Several formulations were used during the pre-clinical and clinical drug development phases. However, in all cases, the formulation consisted of an aqueous solution for IV administration and differences in excipients in the different formulas were minor.

- Distribution

Rizafungin presents a very high plasma protein binding, with unbound fractions in the order of 2.6% in the healthy subjects' plasma. This value increases ~2.7-fold in patients, most likely due to reduced albumin levels common to severe illness.

The volume of distribution determined by non-compartmental analysis in the phase 1 studies was determined to be around 30-50 L in healthy subjects.

- Elimination

After SD and MD administration in the phase 1 studies, a low clearance with long elimination half-life and lack of significant presence of rezafungin in the urine was observed. This was confirmed by the mass-balance

study where, despite the inability to collect all samples required for the full collection of the administered dose, by extrapolation based on later time sample collections, it was concluded that ~74% of the drug was eliminated by the faeces primarily as rezafungin. The remaining was eliminated in the urine primarily as metabolites. Overall, this indicates that the eliminations is mainly by faecal excretion and that metabolism does not seems to be significant either. The applicant did a thoughtful discussion on the possible role of transporters in the biliary/intestinal elimination of rezafungin. Excluding all the tested transporters that rezafungin was shown not to be a substrate, the applicant identified the uptake transporters OSTα/β and/or NTCP, and the efflux transporter BSEP as possible targets. These are not frequently associated with relevant drug transport and no DDI risk is expected. Also, due to the very slow elimination of rezafungin and the high molecular weight of the drug (MW 1226), it is agreed that the most probable explanation for this elimination route is by slow passive diffusion (shown on caco-2 cells) and retention of the drug in the bile (due to the high molecular weight).

Rezafungin was metabolically stable when incubated with hepatocytes from rats, dogs, cynomolgus monkeys, and humans and with liver and intestinal microsomes from rats, dogs (intestinal only), cynomolgus monkeys and humans. It is also chemically stable in phosphate buffered saline. In vivo, and based on the mass balance study, rezafungin AUC accounted for the vast majority (~77%) of the radiocarbon AUC in plasma. Analyses of plasma, urine, and faeces samples indicated that rezafungin underwent minimal metabolism in human subjects to produce 14 metabolites, of which 13 were identified and characterised. Hydroxyrezafungin- metabolites M1241_1, M1241_2, and M1241_3 were the most abundant circulating metabolites. Each of these individual metabolites accounted for less than 10% of the total radioactivity AUC. A biotransformation pathway of rezafungin in humas was proposed.

- Dose proportionality and time dependency

Based on the SD and MD studies, rezafungin exhibits linear kinetics over a range of single (50 – 1400 mg) and multiple doses (100 – 400mg).

The disposition process of rezafungin does not seem to be dependent in a relevant way of any metabolizing or protein transport system. As such, no time dependency is expected in the PK of this drug. This is also confirmed by the in vivo behaviour after MD, where linearity was observed in the range of doses from 100 mg to 400 mg, but also on the similar exposure observed at day 8 and day 15 (dose 2 and 3) after a single 400 mg loading dose on Day 1, followed by 200 mg dose on Day 8 and Day 15, where Steady state is considered achieved with the first loading dose that is twice the weekly maintenance dose (and the elimination half-life is close to one week).

- Intra- and inter-individual variability

Based on the PopPK model, moderate variability was observed in the main PK parameters. This goes in line with the type of administration and the relatively simple disposition process of the drug.

- Pharmacokinetics in target population

Based on sparse data from the clinical phase 2/3 safety and efficacy studies and using the PopPK model, Rezafungin exposure estimates simulated using the population PK model in infected patients and hepatically impaired subjects were approximately 30% lower than the ones observed in healthy subjects. In fact, the covariate included in the final model with the largest impact on exposure was disease state. This covariate results in a reduced CL and V1 for the healthy subjects, explaining the higher exposure in this population. The difference in exposure between healthy subjects and diseased subjects is also likely to reflect inherent albumin differences as well. This difference in not considered clinically relevant.

- Special Populations

No dedicated study was made for assessing the effect of renal impairment in the PK of rezafungin. However, the clinical phase 2/3 safety and efficacy studies have included a significant number of patients with various degrees of renal impairment, including 8 subjects with kidney failure (as assessed by the creatinine clearance). Despite of this, CRCL was not considered a significant covariate explaining the PK variability in the study data. Also, no significantly different exposures were observed between subjects with normal renal function and the various levels of renal impairment that were present in the study. This goes in line with the lack of relevance of the renal process in the elimination of rezafungin, as well as the lack of relevance of transporters in the PK overall process. As such, no need for dose adjustment is required in this group.

A single dose PK study was conducted to assess the pharmacokinetics of rezafungin in subjects with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, in comparison to matched healthy adults with normal hepatic function. Although exposure was approximately 30% lower in subjects with hepatic impairment compared to subjects with normal hepatic function, the mean plasma concentration profiles were similar between subjects with moderate and severe hepatic impairment. Clearance and volume of distribution were higher in subjects with hepatic impairment compared to matched subjects with normal hepatic function. Mean half-life values were generally similar across groups (approximately 110 to 124 hours). Plasma protein binding was similar between subjects with moderate hepatic impairment compared to matched controls with normal hepatic function. The plasma protein binding was lower in subjects with severe hepatic impairment, which may have been reflective of reduced baseline albumin levels in those subjects. In the PopPK model, albumin was included as a covariate describing part of variability in V23. Also, similar exposures were determined for patients and subjects with hepatic impairment. As such, there seems to be no need for dose adjustments in the hepatic impairment.

The PopPK model did not consider gender as a significant covariate of rezafungin PK. Females shown only a slight increase (20%) of the exposure when compared to males.

The PopPK model did not consider race as a significant covariate explaining the variability in the PK parameters. Rezafungin exposures were only slightly increased in Asian subjects, with a 30% increase when compared to white subjects. This is not considered clinically relevant.

Based on the PopPK final model, BSA was a significant covariate explaining part of the variability in CL, V1 and V23. When assessed based on weight or BMI (two covariables highly correlated to BSA), an approximate exposure reduction of around 20% is observed for the obese whereas only a slight increase of 3% is observed for the underweight. These changes are not considered clinically relevant, and no dose adjustment is deemed necessary based on weight.

No dedicated study was performed in the elderly population. However, the data included in the PopPK analysis considered a population with an age ranging from 20 to 89 years with a median age of 53 years. In fact, the PopPK data set considered 38 subjects in the 65-74 years age group, 18 subjects in the 75-84 years age group, and 7 subjects in the >85 years age group. This is acceptable.

Based on the PopPK study age was not considered to be a significant covariate in the final model and have shown no relevant difference on the exposure following a single 400 mg dose in patients enrolled in the phase 2/3 clinical studies.

No data is yet available in the younger population. In this regard a PIP is agreed and results are expected by 2025.

Overall, the pharmacokinetics in special populations are sufficiently characterized.

- DDI

In vivo

The applicant decided to perform two in vivo cocktail DDI studies in healthy subjects. The first study was designed in order to evaluate the effect of rezafungin on several probe substrates of CYP450 enzymes and drug transporter proteins that were predicted to be possible targets of DDI by the in vitro tools. In the first study, the probe drugs were tacrolimus (CYP3A and P-gp) and repaglinide (CYP2C8 and OATP); metformin (OCT-1 and OCT-2 and MATE1 and MATE2), rosuvastatin (BCRP and OATP) and pitavastatin (OATP); caffeine (CYP1A2), efavirenz (CYP2B6), midazolam (CYP3A4), and digoxin (P-gp), administered alone and in combination with rezafungin in a single sequence crossover study. These model drugs are generally accepted for the in vivo assessment of DDI for the respective metabolic or transport systems. In the second study, the probe drugs were cyclosporine, ibrutinib, mycophenolate mofetil, and venetoclax and the DDI risk was assessed because these drugs are likely to be co-administered with rezafungin. No major effects of Rezafungin were observed on the pharmacokinetics of all the co-administered drugs with only a small increase in AUC (approx. 15%) for repaglinide and rosuvastatin, and a small reduction in AUC for tacrolimus and venetoclax of approximately 15 % and 10%, respectively. A small reduction in Cmax for mycophenolate mofetil and ibrutinib of approximately 19 % and 17%, respectively was seen as was a small increase in Cmax (approx. 12 %) of resouvastatin. In all these cases, no change in the administered dose is deemed necessary.

In vitro

Rezafungin was shown to be stable in vitro when incubated with human liver microsomes and hepatocytes, with no metabolites generated by the end of the incubations. Although some metabolites were observed in vivo (both in humans and rat samples) produced primarily by hydroxylation, because of the low clearance (0.3 L/h) and small relevance of these metabolites for the overall elimination process, the PK of rezafungin does not seem to be influenced by other co-administered drugs due to metabolic DDI. Also, Rezafungin was not found to be a substrate of the major drug transporters. As such, the overall potential of Rezafungin for DDI as a victim of metabolic or transporter inhibitors seems low.

Regarding the potential of DDI with Rezafungin as a perpetrator drug for metabolism, an inhibitor effect of rezafungin was seen for CYP2C8 and CYP3A4 for a concentration of 10 uM. The IC50 values were, however, higher than 25 uM. Since the typical Cmax values in patients at a dose of 400 mg are around 18.8 ug/ml (15.3 uM) and the highest fu (observed in patients) is in the order of 6% (equating to a Cmax unbound of 0.9uM), these IC50 values may be clinically relevant. Regarding TDI, this was not observed in vitro. Additionally, no induction potential for cytochrome P450 isoforms CYP1A2, CYP2B6, or CYP3A4 was observed.

Rezafugin was also found to be an inhibitor of P-gp, OATP1B1, OATP1B3, OAT1, OCT2, OCT1, MATE1 and MATE2-K. The lowest IC50 value was seen for MATE1 6.3 uM. Again, considering the expected Cmax,u value, these inhibitions may be clinically relevant. The lack of clinical relevance of these inhibitions, however, was observed in vivo in the two cocktail PK studies.

The potential for Rezafugin be a victim of DDI as a substrate of drug metabolizing enzymes or protein transporters is considered low. Also, the effect of Rezafugin as perpetrator of DDI by inhibiting metabolizing enzymes or protein transporters is also negligible, as predicted by the in vitro studies and observed by the cocktail in vivo studies.

Clinical PD

- Mechanism of action and Primary Pharmacodynamics

The mechanism of action of echinocandins is widely studied and a more thorough assessment on this subject was performed in the non-clinical development and is described in the non-clinical summary.

1,3-β-D-glucan is an essential component of fungal cell walls. Its synthesis is dependent upon the activity of 1,3-β-D-glucan synthase, an enzyme complex in which the catalytic subunit is encoded by FKS1, FKS2, and FKS3 genes. Echinocandins, including rezafungin, inhibit the 1,3-β-D-glucan synthase enzyme complex.

Primary Pharmacodynamic assessment of rezafungin was based mainly in non-clinical in vitro models and in vivo animal models of infection, which is in line with the "Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease" (CHMP/EWP/1343/01 Rev. 1) and the "Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products" (EMA/CHMP/594085/2015).

The activity of rezafungin in animal therapeutic infections established the efficacy of the antifungal in vivo against Candida spp. Rezafungin has been assessed in a broad range of treatment and prophylactic models of candidemia and candidiasis in mice. In single - and multi-dose studies of systemic infections or invasive candidiasis, rezafungin demonstrated significant dose-dependent antifungal efficacy against C. albicans and A. fumigatus. In several studies, rezafungin delivered dose-dependent efficacy in mice for up to 168 hrs when given as a single dose. Against Candida auris, rezafungin demonstrated statistically significantly higher percent survival compared with mice treated with other antifungal drugs or with untreated mice and was efficacious in a mouse model of invasive candidiasis against C. auris.

In prophylactic models of candidiasis against C. albicans, aspergillosis against A. fumigatus, and pulmonary aspergillosis against A. fumigatus, rezafungin efficacy improved when the time between treatment and infection was shortened and when the rezafungin dose was increased. This effect was also observed in Pneumocystis pneumonia models.

Dosing of rezafungin either once daily or once per week in a guinea pig model of dermatophytosis against Trichophyton mentagrophytes showed efficacy against this organism compared with the vehicle-treated controls.

Reduced susceptibility to echinocandins arises from mutations in glucan synthase catalytic subunit-encoding FKS genes (FKS1 for most Candida spp.; FKS1 and FKS2 for C. glabrata) that impact residues comprising "hotspot" (HS) regions of the Fks protein. The frequency of single-step spontaneous mutations conferring some level of reduced susceptibility to rezafungin in C. albicans, C. glabrata, C. krusei, and C. parapsilosis were low and comparable to other echinocandins at 1× MIC, ranging between 10-8 and 10-9. Serial passage of these same strains on antifungal drug gradient plates also demonstrated a low potential for resistance development with rezafungin passage #20 MIC values all ≤1 µg/mL (4 µg/mL for C. parapsilosis). Rezafungin exhibits some degree of cross-resistance to all fks mutations that confer reduced susceptibility to echinocandins.

- Secondary Pharmacodynamics

The effect of rezafungin on the QT interval and other ECG intervals was assessed in healthy adult subjects. The doses of rezafungin administered were 600 mg and 1400 mg and were selected to achieve relevant therapeutic and supratherapeutic exposures, respectively.

In summary, rezafungin at therapeutic and supratherapeutic doses did not result in clinically meaningful QT prolongation and was well tolerated. Additionally, no difference in QTcF interval between males and females was observed.

There were no clinically significant findings in other cardiac parameters, including heart rate, PR interval, and QRS interval, compared to placebo. Echocardiogram results post-dose were normal in all subjects indicating no effect on cardiac contractility or ejection fraction for single doses of rezafungin up to 1400 mg.

- Dose response studies
Pharmacokinetic/pharmacodynamic (PK/PD) studies with rezafungin have been conducted to (a) identify the Pharmacodynamic Index (PDI) that correlates with efficacy and (b) to determine the nonclinical Pharmacodynamic Targets (PDT) for the most common Candida species. These PDTs were then used in PTA analyses to select, and subsequently confirm, the recommended rezafungin dose regimen. During these investigations, rezafungin MIC data used in these studies was determined using the approved CLSI susceptibility testing methodology.

PK/PD studies of rezafungin showed dose proportional efficacy that correlated strongly with free-drug Cmax/MIC and free-drug AUC0-24/MIC ratio, as has been observed with other echinocandins.

An extended dosing PK/PD study showed that rezafungin could deliver seven days of antifungal activity in an established disseminated candidiasis model against the majority of *C. albicans*, *C. glabrata* and *C. parapsilosis* strains tested.

In these studies, efficacy was demonstrated against *C. glabrata* despite two of the three isolates being fks mutants. Rezafungin showed differentiated activity to that of micafungin in a mouse intra-abdominal candidiasis model where superior tissue accumulation was seen. The concentration-dependent mechanism of action, good tissue penetration and long in vivo half-life suggest a potential for high clinical efficacy against *Candida* spp.

- Main studies
For selection of the dose in the Phase 2 study (STRIVE), the PK/PD target was obtained from data generated in a neutropenic mouse model of candidiasis using a single strain of *Candida albicans* for a conservative pharmacodynamic endpoint i.e., 2- log unit drop in CFU, to ensure that, due to the severity of the disease being treated, a sub-therapeutic dose would be unlikely to be chosen. Data from Phase 1 single and multiple ascending dose studies were used to build a Population PK model to predict rezafungin concentrations after IV administration of single and multiple, once weekly doses. The probability of PK/PD target attainment was assessed using Monte Carlo simulations to support the selection of the doses to be tested in Phase 2. The two dose regimens used in Phase 2 (STRIVE), a first dose of 400 mg followed by either 200 mg once weekly or 400 mg once weekly, were both predicted to exceed the nonclinical efficacy target for Candida albicans. Lower dose regimens were not tested due to the risk of underdosing which could lead to treatment failure and potential for generation of resistance. The data described fully in the CSR and briefly in this document indicated little difference in efficacy and safety between rezafungin regimens of 400 mg once weekly and 400 mg in the first week followed by 200 mg once weekly.

Both the dosing regiments from the Phase 2 study (STRIVE) were considered for progression into the Phase 3 study (ReSTORE). The dose selection for the Phase 3 study (ReSTORE) was supported by refined preclinical PK/PD studies and an updated Population PK model that contained patient data. Re-assessment of target attainment, using the updated information, for the two dose regimens used in Phase 2 (STRIVE), predicted both dosing regimens would provide adequate PK/PD target attainment throughout 4 weeks of dosing, up to a MIC of 0.5 mg/L for C. albicans, and up to an MIC of 16 mg/L for C. glabrata. Additionally, target

attainment data indicated that, increasing the follow-on dose from 200 mg to 400 mg, only improved the MIC coverage by one dilution, from the second week of therapy only. However, most of the benefit of antifungal treatment is likely to occur in the first week of therapy. Therefore, given the target attainment analysis and the results of the Phase 2 study (STRIVE) which demonstrated that a dosing regimen of 400/200 mg had a good safety and tolerability profile and was at least as efficacious as caspofungin, it was proposed that this dose (400/200 mg) would to be taken into the Phase 3 study (ReSTORE) as the benefit-risk ratio was considered highest for this dosing regimen.

- Probability of Target Attainment Analysis (PTA)
Following completion of the Phase 3 study (ReSTORE) target attainment analyses were conducted to estimate the probability of achieving PK/PD targets across the range of MIC values for 6 Candida species based on the EUCAST rezafungin susceptibility testing methodology. This was achieved by using simulated exposures (AUC0-168h) from a virtual population of patients created from the final population PK model for rezafungin, developed using data from 5 Phase 1 studies (CD101.IV.1.01, CD101.IV.1.02, CD101.IV.1.06, CD101.IV.1.07, and CD101.IV.1.15), the Phase 2 study (CD101.IV.2.03; STRIVE), and the Phase 3 study (CD101.IV.3.05; ReSTORE) (NC-200), and MIC distributions generated using the EUCAST antifungal susceptibility testing methodology modified for rezafungin susceptibility testing, as dicussed below.

The probability of achieving the nonclinical PK/PD targets for the Candida species across a range of MIC values based on the EUCAST antifungal susceptibility testing methodology modified for rezafungin susceptibility testing (EUCAST methodology) was estimated for a population of virtual patients. A virtual population of 100,000 patients was generated using the final rezafungin population PK model and the distributions of the demographic covariates (determined to be significant predictors of rezafungin PK) of candidemia and/or invasive candidiasis patients enrolled in Studies CD101.IV.2.03 and CD101.IV.3.05. Vectors of covariates were randomly resampled from the observed Phase 2 and Phase 3 distributions and assigned to the 100,000 virtual patients. The virtual patients were assigned the dosing regimen of interest (IV rezafungin: 400 mg for Week 1 followed by 200 mg weekly for 3 weeks). All fixed and random effect parameters were fixed to the final estimates and individual Bayesian estimates of PK parameters were simulated for each patient. Using each simulated patient's Bayesian PK parameters and dose amounts, simulations were performed to obtain AUC0168 after each weekly dose. R software was used to integrate the predicted concentration-time profiles to obtain weekly estimates of AUC0 168. For the purposes of target attainment analyses, AUC0 168 after the first dose was used (Day 1). Free AUC0 168/MIC EUCAST ratios were calculated for the range of MIC values from Candida species collected in patients with candidemia and/or invasive candidiasis enrolled in the STRIVE and ReSTORE studies, using 2.6% as unbound fraction of drug in plasma.

These analyses predicted that, based on achieving the PK/PD target for stasis, exposures produced following a 400 mg dose of rezafungin would be adequate to treat *C. albicans*, *C. tropicalis* and *C. dubliniensis* with rezafungin MICs up to 0.03 mg/L, (8-fold, 2-fold and 4-fold higher than their respective MIC90), and *C. glabrata* up to an MIC of 4 mg/L (512-fold higher than the MIC90).

The applicant did not elaborate on the influence of neutropenia on the PTA analysis performed or discussed the specific PK/PD relationship in this subset of patients.

However, it is acknowledged that there are several reasons why the PK of an anti-infective agent may be somewhat different, including the general state of these patients due to their underlying conditions. There is also the rather different aspect regarding possible efficacy if the same dose is applied to subjects with normal neutrophil counts vs. neutropenia of various degrees. Here, it may be that the duration of treatment to ensure eradication of organisms when there is little or no contribution from the patient's neutrophils is the more critical matter.

Taking into consideration the difficulty in reaching a clear conclusion on adequacy of the currently recommended dose in profound neutropenia, where the drug itself will provide the antifungal effect without any/much help from the host immune system, the CHMP decided not to further pursue this issue.

2.6.4. Conclusions on clinical pharmacology

The mean predicted exposure PK parameters in a virtual population of patients for rezafungin at steady state under the proposed regime are around 665 ug*h/mL and 12 ug/mL for AUCss,0-168 and Css,max, respectively. Overall, the pharmacokinetics of rezafungin are sufficiently well characterized and only minor Other Concerns left for clarification, regarding the number of patients with ages from 65-74, 75-84 and >85 years that were included in the clinical trials, as well as some further VPCs on the provided PopPK model are requested.

Most of the characterization of the primary pharmacodynamics of rezafungin has been performed in the non-clinical setting (*in vitro* experiments and in animal models of disease). The primary and secondary pharmacodynamics of rezafungin were considered to be sufficiently characterised.

2.6.5. Clinical efficacy

Two controlled clinical studies have been carried out to investigate the efficacy of rezafungin in the treatment of invasive candidiasis:

A Phase 2 (STRIVE) multicentre, randomised, double-blind study to assess safety, tolerability, and efficacy of rezafungin versus caspofungin with optional oral fluconazole step-down therapy in the treatment of subjects with candidemia and/or IC.

Only one Phase 3 pivotal study supported by the results of the Phase 2 study is presented.

A Phase 3 (ReSTORE) multicentre, randomised, double-blind study of the efficacy and safety of rezafungin versus caspofungin with optional oral fluconazole step-down therapy in the treatment of subjects with candidemia and/or IC.

- **Tabular Description of Clinical studies**

Study	Study Centres and Locations	Study Start and End Dates, and Enrolment Status	Design, Study Population	Study and Control Drugs, Dose, Route, and Regimen	Subjects per Treatment Arm, Sex and Median Age (Range)	Primary Endpoint(s)
CD101.IV.2.03 STRIVE	43 sites across 10 countries (Belgium, Bulgaria, Canada, Greece, Hungary, Italy, Romania, Russia, Spain, United States)	26 Jul 2016; Completed; 18 Apr 2019; 207 enrolled[a]	Phase 2 Randomised Double-blind Subjects with Candidemia and/or IC	Group 1: Rezafungin 400 mg on Day 1 and Day 8; optional Day 15 400 mg dose; subjects with IC, Day 22 optional 400 mg dose. Group 2: Rezafungin 400 mg on Day 1, 200 mg on Day 8; Day 15 optional 200 mg dose; subjects with IC, Day 22 optional 200 mg dose. Caspofungin: 70 mg dose on Day 1 and then 50 mg/day, up to a maximum of 21 days (subjects with candidemia only), or 28 days (subjects with IC). After ≥3 days of IV therapy, subjects could be switched to oral step-down therapy beginning on Day 4 (fluconazole for the caspofungin group, or fluconazole placebo for the rezafungin group). The minimum duration of treatment was 14 days (IV plus optional oral therapy).	Group 1: 81 total 44 M/37 F 61.0 years (24.0–88.0) Group 2: 57 total 36 M/21 F 63.0 years (24.0–91.0) Caspofungin: 69 total 38 M/31 F 63.0 years (24.0–93.0)	Overall, Success at Day 14 Safety/tolerability
CD101.IV.3.05 ReSTORE	66 sites across 15 countries (Australia, Belgium, Bulgaria, China, Colombia, Spain, France, Greece, Israel, Italy, South Korea, Singapore, Thailand, Taiwan, USA)	12 Oct 2018; Completed; 11 Oct 2021; 199 enrolled to achieve 184 mITT	Phase 3 Randomised Double-blind Subjects with Candidemia and/or IC	Rezafungin 400 mg on Day 1, 200 mg on Day 8; an optional 200 mg dose on Day 15 and Day 22. Caspofungin 70 mg loading dose on Day 1 and then 50 mg/day up to a maximum of 28 days. After ≥3 days of IV therapy, subjects could be switched to oral step-down therapy (fluconazole for the caspofungin group, or fluconazole placebo for the rezafungin group). The minimum duration of treatment was 14 days (IV plus optional oral therapy).	Rezafungin: 100 total 67 M/33 F 59.0 years (19–89) Caspofungin: 99 56 M/43 F 62.0 years (20–91)	Global Cure at Day 14 (±1 day) – primary endpoint for EMA All-cause Mortality at Day 30 (-2 days) – primary endpoint for FDA

2.6.5.1. Dose response study

- STRIVE

The Phase 2 STRIVE study was a multicentre, prospective, randomised, double-blind study of rezafungin compared with intravenous (IV) caspofungin for treatment of adult subjects (≥ 18 years) with candidemia and/or IC, reflective of the target population. After ≥3 days of IV caspofungin therapy, if step-down criteria were met, subjects could be switched to oral fluconazole therapy.

The primary efficacy outcome was Overall Response at Day 14 defined as mycological eradication AND resolution of attributable systemic signs of candidemia and/or IC that were present at baseline, no change of antifungal therapy for the treatment of candidemia and/or IC, and the subject was not lost to follow-up on the day of assessment. The possible signs of infection that might be attributable to candidemia and/or IC at baseline included fever, hypothermia, hypotension, tachycardia, and tachypnoea.

Secondary objectives included overall success at other timepoints, mycological success, clinical cure as assessed by the Investigator, and the PK of rezafungin.

This study has two parts - Part A and Part B.

In Part A, subjects were randomised 1:1:1 to the following groups:

- Group 1: rezafungin 400 mg on Day 1 and Day 8; an optional 400 mg dose on Day 15; and for subjects with IC, an optional 400 mg dose on Day 22. Referred to as rezafungin 400/400 mg. Subjects in Group 1 received IV saline (placebo for caspofungin) on other study days to maintain the blind. Subjects who had already switched to oral step-down therapy received both oral placebo (for fluconazole) daily and rezafungin IV on Day 8 and Day 15 for subjects who required >14 days of therapy, and Day 22 for subjects with IC (with or without candidemia) who required >21 days of therapy.
- Group 2: rezafungin 400 mg on Day 1, 200 mg on Day 8; an optional 200 mg dose on Day 15; and for subjects with IC, an optional 200 mg dose on Day 22. Referred to as rezafungin 400/200 mg. Subjects in Group 2 received IV saline (placebo for caspofungin) on other study days to maintain the blind. Subjects who had already switched to oral step-down therapy received both oral placebo (for fluconazole) daily and rezafungin IV on Day 8 and Day 15 for subjects who required >14 days of therapy, and Day 22 for subjects with IC (with or without candidemia) who required >21 days of therapy.
- Caspofungin IV: 70 mg loading dose on Day 1 and then 50 mg/day up to a maximum of 21 days for subjects with candidemia only, or up to a maximum of 28 days for subjects with IC. After ≥3 days of IV therapy, subjects in the caspofungin group could be switched to oral step-down therapy with fluconazole (800 mg on the first day, followed by 400 mg daily thereafter). The minimum duration of treatment was 14 days (IV plus optional oral step-down therapy). To maintain the blind, subjects who had already switched to oral step-down therapy received both oral fluconazole daily and IV saline placebo (for rezafungin) on Day 8 and Day 15 for subjects who required >14 days of therapy, and Day 22 for subjects with IC (with or without candidemia) who required >21 days of therapy.

In Part B, subjects enrolled under Protocol Amendment 5 (n=69) were randomised in a 2:1 ratio to rezafungin Group 1 or caspofungin (termed Part B1 for analysis), and subjects enrolled under Protocol Amendment 6 (n=31) were randomised in a 2:1 ratio to rezafungin Group 2 or caspofungin (termed Part B2 for analysis). The purpose of Part B was to further assess the safety and efficacy of rezafungin. Following evaluation of the unblinded results from Part A, it was determined that the optimum rezafungin dose regimen for Phase 3 was the 400 mg dose in Week 1 followed by 200 mg once weekly for a total of 2 to 4 weeks (Group 2).

STRIVE was an exploratory study not powered for inferential statistical analyses. A sufficient number of subjects were randomised in Part A to provide substantive analysis of safety, tolerability, and estimate efficacy.

Assessments of mycological eradication and clinical response were performed on Day 5 and Day 14; on Day 28 for subjects with IC; and at the Follow-up visit (Days 45–52 for subjects with candidemia only or Days 52–59 for subjects with IC with or without candidemia). Blood cultures were performed daily or every other day until 2 blood cultures drawn ≥12 hours apart were negative without an intervening positive culture.

Approximately 114 subjects in Part A were planned to be randomized given an estimated discontinuation rate of 20%, in order to achieve 90 evaluable subjects in the mITT population. In Part A, assuming a 73% overall success rate, the sample size of 30 subjects in the mITT population in each rezafungin treatment group and the IV caspofungin group would yield a 95% confidence interval (CI) for this success rate of 53.8% to 87.5%.

The following analysis populations were defined:

- Intent-to-Treat (ITT): all subjects randomized to treatment.
- Safety: all subjects randomized to treatment and who received any amount of study drug.

- mITT: A subset of the Safety Population with documented *Candida* infection based on a Central Laboratory (CL) evaluation of an isolate from a blood culture obtained within 96 hours of randomization or from a specimen obtained from a normally sterile site.
- mITT2: A subset of subjects in the mITT Population who had documented *Candida* infection based on CL evaluation of a culture from blood drawn within 12 hours prior to randomization or within 72 hours after randomization or a culture from another normally sterile site obtained within 48 hours prior to randomization or within 72 hours after randomization.
- mITT3: A subset of subjects in the mITT Population who had documented *Candida* infection based on CL evaluation of a culture from blood drawn within 12 hours prior to randomization or within 72 hours after randomization or a culture from another normally sterile site obtained within 96 hours prior to randomization or within 72 hours after randomization.
- PK: all rezafungin-treated subjects with at least 1 plasma sample obtained for PK analysis.

The subsets of mITT (mITT2 and mITT3) were analysed in response to concerns raised by the EMA during scientific advice regarding the timing of culture sampling in relation to randomisation and the impact on the interpretability of the results (EMA/CHMP/SAWP/596942/2018).

For Part A, of 115 subjects screened for enrolment, 107 were randomized, and 73 (68.2%) completed the study. The primary reason for discontinuation from the study was death (overall 12.1%) and the rate in the caspofungin group was somewhat higher (16.7%), compared with the rezafungin groups (8.6% and 11.1% for Groups 1 and 2, respectively). The rate of discontinuation from the study due to a study drug-related AE was low (2.8%, 2 subjects in Group 1 and 1 subject in caspofungin).

For Part B, of 104 subjects screened for enrolment, 100 were randomized, and 75 (75%) completed the study. The primary reason for discontinuation from the study was death (overall 16.0%) and the incidence was similar across treatment groups. Other reasons for discontinuation from the study included lost to follow up (4.0%) and withdrawal by subject (4.0%).

Three interim analyses were performed: a blinded review of safety data of Group 1 subjects which determined that stopping criteria were not met; an unblinded review of selected efficacy and safety data for 70 subjects in Part A; and an unblinded review of all parameters for 107 subjects in Part A.

Of subjects randomized in Part A, 97.2% received at least 1 dose of study drug and 86.0% were included in the mITT Population; in Part B, 98.0% received at least 1 dose of study drug and 91.0% were included in the mITT Population. The mITT2 and mITT3 Populations were approximately a third of the size of the ITT Population.

The ITT Population for Parts A and B combined was largely male (57.0%), White (83.1%), and not Hispanic or Latino (86.0%), with a mean age of 59.6 years (range 24 to 93) and a diagnosis of candidemia only (79.2%). For all subjects, the mean estimated normalized creatinine clearance was 84.9 mL/min and mean APACHE II score was 13.8 (range 1 to 35) with nearly half of subjects in the 10-19 category (49.3%).

Demographic and baseline characteristics were similar across groups except for mean estimated normalized creatinine clearance in Group 2 (72.8 in Group 2 versus 84.9 total). While mean APACHE II scores were similar across groups, incidence of severe APACHE II scores (≥20) at baseline was somewhat higher in the rezafungin groups (21.0% to 24.6%) compared with the caspofungin group (13.0%).

Primary endpoint

For the primary efficacy outcome of Overall Success at Day 14, the number and percentage of subject treatments programmatically determined to be an overall success, failure, or with an indeterminate overall response were summarised by treatment group for subjects in the mITT Population. Exact 2-sided 95% CIs for the percentage of subjects who achieved success in each treatment group were determined using the Clopper-Pearson method.

A summary of overall response at Day 14 was provided for Parts A and B combined in the mITT2 and mITT3 Populations and for subjects in the mITT2 and mITT3 Populations without prior antifungal therapy.

Success rates were high in all treatment groups with rates of 76.1% in Group 2, 60.5% in Group 1, and 67.2% in caspofungin. However, the rate of indeterminate response in Group 1 (13.2%) was more than double that of Group 2 (6.5%) or caspofungin (4.9%), contributing to the comparatively lower rate of success in Group 1. The failure rates were 17.4%, 26.3% and 27.9% for Group 2, Group 1, and caspofungin, respectively.

The most common reason for failure in all groups was mycological failure, and the rate of failure attributed to mycological failure was 21.3% in the caspofungin group, 15.8% in Group 1 and 13.0% in Group 2. The reasons for an indeterminate response were considered unrelated to the study drug.

Table 20. Overall Response at Day 14 (mITT Population)

	Statistic	Rezafungin 400 mg/400 mg Group 1 (N=76)	Rezafungin 400 mg/200 mg Group 2 (N=46)	Caspofungin (N=61)
Success	n (%)	46 (60.5)	35 (76.1)	41 (67.2)
	95% CI	48.6, 71.6	61.2, 87.4	54.0, 78.7
Failure/Indeterminate	n (%)	30 (39.5)	11 (23.9)	20 (32.8)
Failure	n (%)	20 (26.3)	8 (17.4)	17 (27.9)
Indeterminate	n (%)	10 (13.2)	3 (6.5)	3 (4.9)

Source: Table 14.2.1.1C, Listing 16.2.6.1.
Abbreviations: CI=confidence interval; N=number of subjects in the mITT Population; n=number of subjects in the specified category.

Table 23. Reasons for Failure or Indeterminate Overall Response at Day 14 (mITT Population)

Overall Response	Reason	Statistic	Rezafungin 400 mg/400 mg Group 1 (N=76)	Rezafungin 400 mg/200 mg Group 2 (N=46)	Caspofungin (N=61)
Failure		**n**	20	8	17
	Death	n (%)	7 (9.2)	2 (4.3)	4 (6.6)
	Mycological failure	n (%)	12 (15.8)	6 (13.0)	13 (21.3)
	Recurrence of attributable SS	n (%)	2 (2.6)	0	2 (3.3)
	Fever	n/N1 (%)	1/39 (2.6)	0/18 (0.0)	1/31 (3.2)
	Hypothermia	n/N1 (%)	0/ 1 (0.0)	0/ 2 (0.0)	0/ 1 (0.0)
	Hypotension	n/N1 (%)	1/15 (6.7)	0/11 (0.0)	1/14 (7.1)
	Tachycardia	n/N1 (%)	2/52 (3.8)	0/25 (0.0)	1/37 (2.7)
	Tachypnea	n/N1 (%)	1/44 (2.3)	0/26 (0.0)	1/34 (2.9)
Indeterminate		n	10	3	3
	Inadequate number of mycological cultures	n (%)	7 (9.2)	3 (6.5)	2 (3.3)
	Assessment of SS not completed	n (%)	6 (7.9)	2 (4.3)	1 (1.6)
	Attributable SS not reported at baseline	n (%)	1 (1.3)	0	0

Source: Table 14.2.1.2C, Listing 16.2.6.1, 16.2.6.2.
Abbreviation: N=number of subjects in the mITT Population; n=number of subjects in the specified category; N1=number of subjects with the specified sign at baseline; SS=systemic signs.
Note: Reasons for failure or indeterminate response are not mutually exclusive.
Note: Mycological failure includes subjects with a change in antifungal therapy for the treatment of candidemia and/or IC.

Success rates in the mITT2 Population were 57.5% (23/40), 86.7% (13/15), and 68.0% (17/25), and in the mITT3 Population were 55.3% (26/47), 88.9% (16/18), and 70.4% (19/27) in Group 1, Group 2, and caspofungin, respectively. Compared with the success rates in the mITT Population, rates in the mITT2 and mITT3 Populations were similar for Group 1 and caspofungin; although higher for Group 2, the sample size in this group was smaller.

Secondary endpoints

Three secondary outcomes:

1) Overall Success at Day 5, Day 28 (±2) and Follow-up

2) Mycological Success at Day 5, Day 14 (±1), Day 28 (±2) and Follow-up

3) Investigator's Assessment of Clinical Response at Day 14 (±1), Day 28 (±2), and the Follow-up Visit

For these, the number and percentage of subjects with an overall success, failure, and indeterminate response at the pre-specified time (above) were summarized by treatment group for subjects in the mITT population. Exact 2-sided 95% CIs for the percentage of subjects who achieve success in each treatment group were determined using the Clopper-Pearson method. If the number of subjects with IC overall is <10, 95% CI will not be provided for the percentage of subjects who achieve success. These analyses will be conducted for Part A, Part B, and for Parts A and B combined.

1) Overall Response at Day 5 and Follow-Up

Overall response (success) was 60.5%, 76.1%, and 67.2% in the rezafungin group 1, group 2 and caspofungin group, respectively. The number of indeterminate responses in rezafungin Group 1 was 13.2%, versus 4.3% and 4.9% in the rezafungin Group 2 and caspofungin groups, respectively. The true failure rate (i.e., without the indeterminate responses included) was 31.6% in the rezafungin Group 1, 21.7% in the rezafungin Group 2, and 39.3% in the caspofungin group.

2) Mycological Response

At Day 5, the rate of success (eradication) in mycological response in rezafungin treatment Group 1 was 65.8% and rezafungin Group 2 was 76.1%. The success rate in caspofungin was 62.3%. However, the rate of indeterminate mycological response in Group 1 (11.8%) was more than double that of Group 2 (4.3%) and caspofungin (3.3%). Failure rate was higher in the caspofungin group (34.4%) compared with Group 2 (19.6%) and Group 1 (22.4%).

At Day 14, the rate of success (eradication) in mycological response in rezafungin treatment was unchanged, with Group 1 at 65.8% and Group 2 at 76.1%. The success rate in caspofungin increased to 68.9%.

Mycological success (eradication) rates were highest in Group 2 compared with other groups at Day 5, Day 14, and at the Follow-up Visit.

Similarly, at Day 5 in subjects with candidemia only, the rate of indeterminate mycological response in Group 1 (10.5%) was higher than that of Group 2 (5.6%) and caspofungin (4.2%). Failure rate was higher in the caspofungin group (37.5%) compared with Group 1 (17.5%) and Group 2 (19.4%).

At Day 14, the rate of indeterminate mycological response in Group 1 (9.2%) was higher than that of Group 2 (6.5%) and caspofungin (3.3%). Failure rate was higher in the caspofungin group (27.9%) compared with Group 2 (17.4%) and Group 1 (25.0%). In subjects with candidemia only, at Day 14 the rate of indeterminate mycological response and the rate of mycological success were more similar across groups.

3) Investigator's Assessment of Clinical Response

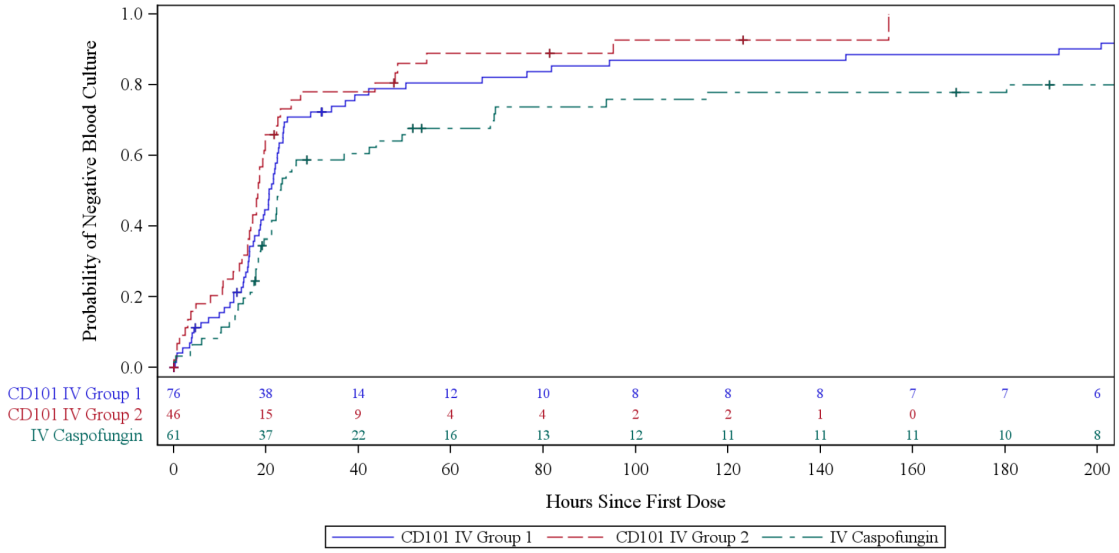
In the mITT population, clinical cure rates were 69.7% in Group 1, 80.4% in Group 2, and 70.5% in caspofungin. The indeterminate rates were similar between the groups (6.6%, 6.5%, and 1.6%, respectively), although the failure rate in Group 2 (13.0%) was half that of Group 1 and caspofungin groups (23.7% and 27.9%, respectively).

Other analysis

Time to Negative Blood Culture

Median time (hours) from first study drug dose to a negative blood culture was 19.5 hours in the combined rezafungin groups compared with 22.8 hours in the caspofungin group.

Figure 3 **Time to Negative Blood Culture Kaplan-Meier Curve (mITT Population).** Source: Figure 14.2.6.1, Table 14.2.6.1C.



Overall Success at Day 14 by Baseline Candida Species

The most prevalent *Candida* species at baseline were *C. albicans, C. glabrata, C. parapsilosis*, and *C. tropicalis*. For these 4 species, overall success rates in Group 2 were >70%. For caspofungin, overall success rates were >70% for *C. albicans, C. glabrata,* and *C. tropicalis.* Group 1 success rates are confounded due to the high number of indeterminate responses. Relatively few *Candida* spp. isolated had a high MIC to rezafungin, caspofungin, or fluconazole.

Table 34. Overall Success at Day 14 by Baseline *Candida* Species (mITT Population); n/N1 (%)

Candida Species at Baseline	Rezafungin 400 mg/400 mg Group 1 (N=76)	Rezafungin 400 mg/200 mg Group 2 (N=46)	Caspofungin (N=61)
Candida albicans	19 /38 (50.0)	14 /19 (73.7)	25 /34 (73.5)
Candida dubliniensis	4 / 4 (100.0)	0 / 0	1 / 1 (100.0)
Candida fermentati	0 / 0	0 / 0	1 / 1 (100.0)
Candida glabrata	12 /13 (92.3)	11 /14 (78.6)	7 /10 (70.0)
Candida guilliermondii	2 / 2 (100.0)	0 / 0	0 / 0
Candida intermedia	0 / 0	0 / 0	0 / 1
Candida kefyr	0 / 0	0 / 0	1 / 1 (100.0)
Candida krusei	0 / 1	2 / 3 (66.7)	1 / 1 (100.0)
Candida metapsilosis	0 / 0	1 / 1 (100.0)	0 / 0
Candida parapsilosis	6 /10 (60.0)	6 / 7 (85.7)	4 /11 (36.4)
Candida rugosa	0 / 1	0 / 0	0 / 0
Candida tropicalis	4 / 9 (44.4)	5 / 7 (71.4)	5 / 6 (83.3)
Candida utilis	1 / 1 (100.0)	0 / 0	0 / 0

Source: Table 14.2.7.1.1C, Listing 16.2.4.6.2, 16.2.6.1.
Abbreviation: N=number of subjects in the mITT Population; n=number of subjects in the specified category; N1=number of subjects with the specified *Candida* pathogen.

Although sample size was small, overall success rates remained high at the highest MIC for rezafungin for *C. albicans*. However, Group 1 outcomes may be confounded due to the high number of indeterminate responses. Rezafungin appeared to work as well in *C. parapsilosis* as it did in other species, and perhaps better than caspofungin, but the population sizes are small. Relatively few *Candida* isolates had a high MIC to rezafungin, caspofungin, or fluconazole.

The Phase 2 study STRIVE provided additional information for the dose selection for the Phase 3 trial. The primary endpoints chosen for the two trials are different as the primary objective of the Phase 2 study lacks the component of radiological cure; this precludes an integrated analysis for this endpoint.

2.6.5.2. Main study

- ReSTORE

Methods

The Phase 3 ReSTORE study was a multicentre, randomised, double-blind study to evaluate the efficacy and safety of IV rezafungin versus IV caspofungin with optional oral fluconazole step-down in the treatment of subjects with candidemia and/or IC.

Study participants

Eligible subjects were to have a mycological diagnosis of candidemia and/or invasive candidiasis and one or more systemic signs (e.g., fever, hypothermia, hypotension, tachycardia, tachypnoea, local signs of inflammation) attributable to these conditions. The mycological diagnosis was defined as:

a. ≥ 1 blood culture positive for yeast or *Candida* OR

b. Positive test for *Candida* from a Sponsor-approved rapid IVD OR

c. Positive Gram stain (or other method of direct microscopy) for yeast or positive culture for *Candida* spp. from a specimen obtained from a normally sterile site.

Per protocol, patients with the following forms of invasive candidiasis were excluded:

a. Septic arthritis in a prosthetic joint (septic arthritis in a native joint is allowed)

b. Osteomyelitis

c. Endocarditis or myocarditis

d. Meningitis, endophthalmitis, chorioretinitis, or any central nervous system infection

e. Chronic disseminated candidiasis

f. Urinary tract candidiasis due to ascending *Candida* infection secondary to obstruction or surgical instrumentation of the urinary tract

Although *in vitro* diagnostic tests were permitted for mycological diagnosis, only blood and specimens from normally sterile sites were used.

Treatments

Subjects that were successfully enrolled were randomised to a treatment in a 1:1 ratio, to receive either rezafungin or caspofungin. Subjects randomised to rezafungin were to receive a 400 mg dose in Week 1, followed by 200 mg once weekly, for a total of 2 to 4 doses. Subjects randomised to caspofungin were to receive a total treatment of ≥14 days beginning with a single caspofungin 70 mg IV loading dose on Day 1 followed by caspofungin 50 mg IV once daily with the option to continue treatment ≤28 days. After ≥3 days IV treatment (or the minimum duration of IV therapy advised by the site's national/regional/local guidelines, whichever was greater), subjects could be switched to oral step-down fluconazole/placebo therapy by the Investigator if they met the oral step-down therapy criteria. IV or oral placebos were used as required throughout the study to maintain the blind.

The chosen comparator is approved in the treatment of invasive candidiasis. The use of IV and oral placebos is acceptable in the context of a non-inferiority trial.

Objectives

The primary objective of this study was to:

Demonstrate that rezafungin for injection is noninferior to caspofungin for global cure (clinical cure as assessed by the Investigator, radiological cure [for qualifying invasive candidiasis subjects], and mycological

eradication, as confirmed by the Data Review Committee [DRC]) at Day 14 (±1 day) in the mITT Population (European Medicines Agency [EMA] primary objective)

The three individual components of the EMA primary objective were included separately as secondary objectives, as recommended by the EMA (EMEA/H/SA/3888/1/2018/III).

All-cause mortality (ACM) at Day 30 (-2 days) in the modified Intent-to-Treat (mITT) Population was also considered as a secondary objective (primary objective for the US Food and Drug Administration [FDA]).

The primary objective is in accordance with Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease (CHMP/EWP/1343/01).

Outcomes/endpoints

The primary efficacy outcome for the Phase 3 ReSTORE study was global cure (based on clinical cure as assessed by the Investigator, radiological cure [for qualifying IC subjects], and mycological eradication) confirmed by a blinded independent DRC at Day 14 (±1 day).

Secondary efficacy outcome measures were:

- ACM at Day 30 (-2 days). All attempts were to be made to determine the survival status of all subjects at Day 30. However, if it was unknown whether a subject was alive or deceased, the subject was considered deceased for the primary efficacy outcome. Note that ACM was the primary endpoint for the US FDA
- Global cure (as confirmed by the DRC) for subjects receiving rezafungin for injection and caspofungin at Day 5, Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59) visit in the mITT Population
- Mycological eradication for subjects receiving rezafungin for injection and caspofungin at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59) visit in the mITT Population
- Clinical cure as assessed by the Investigator for subjects receiving rezafungin for injection and caspofungin at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59) visit in the mITT Population
- Radiological cure for IC subjects receiving rezafungin for injection and caspofungin at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59) in the mITT Population

The exploratory outcome was:

- Compare resolution of systemic signs attributable to candidemia and/or IC for subjects receiving rezafungin for injection and caspofungin at Day 5, Day 14 (±1 day), Day 30 (-2 days) and Follow--up Days (52–59) in the mITT Population

The chosen endpoints are aligned with the objectives.

Sample size

Sample size justification for the Primary Efficacy Outcome EMA (Global cure): Using a 20% NI margin, one-sided alpha of 0.025, 80% power, 1:1 randomization, a global cure rate of 70% in both the Rezafungin for Injection and caspofungin groups, and the sample size methodology based on a continuity corrected Z-statistic, a total of 184 subjects (92 subjects in each treatment group) are required in the mITT population. Assuming 85% of subjects would be evaluable for the mITT population, a total of approximately 218 subjects would be randomized.

The applicant took scientific advice (SA) on 06/12/2017. The company was advised at the time that the proposed NI margin of 20% was too wide; a proposed margin of 10% to 11% was considered to be more in line with such products.

Randomisation and blinding (masking)

An Interactive Response Technology was used to randomise subjects. Randomisation was in a 1:1 ratio to each treatment arm and it was stratified based on diagnosis (candidemia only; invasive candidiasis) and by Acute Physiology and Chronic Health Evaluation (APACHE II) score/absolute neutrophil count (ANC) (APACHE II score ≥ 20 OR ANC < 500 cells/µL; APACHE II score < 20 AND ANC ≥ 500 cells/µL) at screening.

ReSTORE was double blind and active controlled (caspofungin with a potential switch to oral step-down fluconazole therapy).

Statistical methods

Analysis populations

- The ITT Population includes all randomised subjects.
- The Safety Population includes all subjects who received any amount of the study drug. Safety analyses were performed on the Safety Population. Subjects who received the wrong study drug for their entire course of study drug were analysed in the treatment group based on the drug received. Subjects who received the wrong study drug for part of their course of study drug were analysed in the treatment group based on majority of (i.e., most frequent) doses received.
- The mITT Population includes all subjects who had a documented *Candida* infection based on central laboratory evaluation of a blood culture or a culture from a normally sterile site obtained ≤4 days (96 hours) before randomisation and received ≥1 dose of study drug.
- The Clinically Evaluable Population includes all subjects in the mITT Population who also met inclusion criterion #4, did not meet exclusion criteria #1, #2, and #5, had an assessment of both mycological and clinical response at Day 14 in the protocol-specified window of Day 14 ±1 day (subjects with IC documented by radiologic/imaging evidence also must have had an assessment of radiological response), and did not have any other factor that could confound the assessment of the Global Response at Day 14.
- The PK Population includes all subjects who received any amount of study drug and had at least one blood sample with measurable concentrations.

Given that a proportion of subjects with a positive culture from blood taken up to 96 h before randomisation could already be culture negative at the time of study drug administration, a pre-defined subgroup analysis was undertaken in two further populations, with the intent of assessing the efficacy of rezafungin treatment commenced when subjects have ongoing IC, hereby denoted as mITT2 and mITT3:

mITT2:

All subjects who received ≥1 dose of study drug and had documented *Candida* infection based on central laboratory evaluation of:

- a culture from blood drawn within 12 hours prior to randomisation or within 72 hours after randomisation, OR
- a culture from another normally sterile site obtained within 48 hours prior to randomisation or within 72 hours after randomisation

mITT3:

All subjects who received ≥1 dose of study drug and had documented Candida infection based on central laboratory evaluation of:

- a culture from blood drawn within 12 hours prior to randomisation or within 72 hours after randomisation, OR
- a culture from another normally sterile site obtained within 96 hours prior to randomisation or within 72 hours after randomisation

Primary Efficacy Analysis

The primary efficacy outcome for the EMA was global cure (DRC confirmed) at Day 14 (±1 day) in the mITT Population. The number and percentage of subjects in each treatment group who had a global response of cure, failure, or indeterminate, was presented by treatment group at Day 14 (±1 day) in the mITT Population. An adjusted (for the randomisation stratification factors) two-sided 95% CI for the observed difference in the global cure rate (rezafungin group minus caspofungin group) was calculated using the method of Miettinen and Nurminen. If the lower bound of the 95% CI was greater than -20%, non-inferiority of rezafungin was concluded.

Subgroup analyses of mortality through 30 days (-2 days) and global response at Day 14 (±1 day) were performed to investigate the consistency of the treatment effects for different groups of subjects. All-cause mortality and global response at Day 14 (±1 day) were assessed separately within the following subgroups in the mITT Population: sex (male vs female), race (White vs non-White, and Asian vs non-Asian), age category (<65 years vs ≥65 years), geographic region (United States/South America, Europe/Israel/Turkey, Asia-Pacific [excluding China/Taiwan], China/Taiwan), diagnosis at randomization (candidemia only vs invasive candidiasis), final diagnosis (candidemia only vs invasive candidiasis: progression from candidemia only to invasive candidiasis was determined based on the radiological and/or tissue/fluid culture assessment through Day 14), and APACHE II score/ANC at Screening (APACHE II score ≥20 OR ANC <500 cells/μL versus APACHE II score <20 AND ANC ≥ 500 cells/μL), APACHE II score at Screening (≥20, <20, 10–19, <10), ANC at Screening (<500 cells/μL vs ≥500 cells/μL). All-cause mortality through 30 days (-2 days) and global

response at Day 14 (±1 day) were also summarized in the subgroups defined by timing of the culture used to document the *Candida* infection.

Secondary Efficacy Analyses

For ACM, the number and percentage of subjects in each treatment group who were alive and deceased/unknown survival status at Day 30 (-2 days) was determined in the mITT Population. A two-sided 95% CI for the observed difference in the ACM rate (rezafungin group minus caspofungin group) was calculated using the unadjusted method of Miettinen and Nurminen. If the upper bound of the 95% CI was lower than 20%, non-inferiority of rezafungin was concluded.

The number and percentage of subjects with a global response of cure, failure, or indeterminate was presented by treatment group in the mITT Population at Day 5, Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59).

The number and percentage of subjects with a mycological response of eradication, failure, or indeterminate was presented by treatment group in the mITT Population at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59).

The number and percentage of subjects with a clinical response of cure, failure, or indeterminate was presented by treatment group in the mITT Population at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59).

For subjects with IC documented by radiologic/imaging evidence with a radiological cure, failure, or indeterminate was presented by treatment group in the mITT Population at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59).

The 95% CIs for the treatment differences in global cure, mycological eradication, clinical cure as assessed by the Investigator, and radiological cure, were determined.

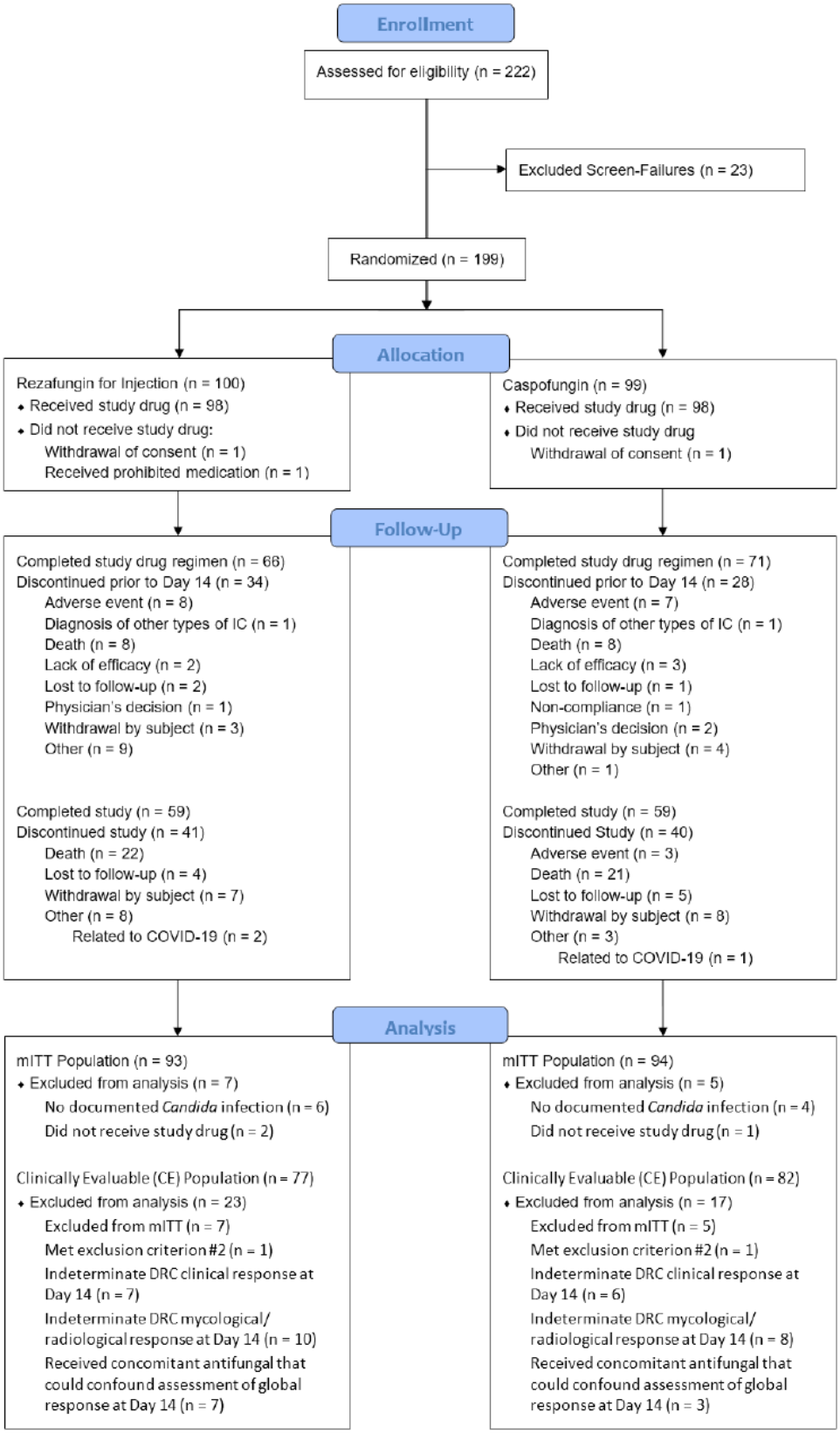
Missing Data

Subjects with missing outcome data are considered to have an indeterminate response. Subjects with an indeterminate response are included in the denominator of the response calculation and thus, are treated in the same manner as failures in the analysis. In general, there will be no substitutions made to accommodate missing data points.

Results

- **Participant flow**

Subject disposition is summarised in the diagram below.


Enrollment
Assessed for eligibility (n = 222)
Excluded Screen-Failures (n = 23)
Randomized (n = 199)
Allocation
Rezafungin for Injection (n = 100)
• Received study drug (n = 98)
• Did not receive study drug:
Withdrawal of consent (n = 1)
Received prohibited medication (n = 1)
Caspofungin (n = 99)
• Received study drug (n = 98)
• Did not receive study drug
Withdrawal of consent (n = 1)
Follow-Up
Completed study drug regimen (n = 66)
Discontinued prior to Day 14 (n = 34)
Adverse event (n = 8)
Diagnosis of other types of IC (n = 1)
Death (n = 8)
Lack of efficacy (n = 2)
Lost to follow-up (n = 2)
Physician's decision (n = 1)
Withdrawal by subject (n = 3)
Other (n = 9)
Completed study (n = 59)
Discontinued study (n = 41)
Death (n = 22)
Lost to follow-up (n = 4)
Withdrawal by subject (n = 7)
Other (n = 8)
Related to COVID-19 (n = 2)
Completed study drug regimen (n = 71)
Discontinued prior to Day 14 (n = 28)
Adverse event (n = 7)
Diagnosis of other types of IC (n = 1)
Death (n = 8)
Lack of efficacy (n = 3)
Lost to follow-up (n = 1)
Non-compliance (n = 1)
Physician's decision (n = 2)
Withdrawal by subject (n = 4)
Other (n = 1)
Completed study (n = 59)
Discontinued Study (n = 40)
Adverse event (n = 3)
Death (n = 21)
Lost to follow-up (n = 5)
Withdrawal by subject (n = 8)
Other (n = 3)
Related to COVID-19 (n = 1)
Analysis
mITT Population (n = 93)
• Excluded from analysis (n = 7)
No documented Candida infection (n = 6)
Did not receive study drug (n = 2)
Clinically Evaluable (CE) Population (n = 77)
• Excluded from analysis (n = 23)
Excluded from mITT (n = 7)
Met exclusion criterion #2 (n = 1)
Indeterminate DRC clinical response at Day 14 (n = 7)
Indeterminate DRC mycological/ radiological response at Day 14 (n = 10)
Received concomitant antifungal that could confound assessment of global response at Day 14 (n = 7)
mITT Population (n = 94)
• Excluded from analysis (n = 5)
No documented Candida infection (n = 4)
Did not receive study drug (n = 1)
Clinically Evaluable (CE) Population (n = 82)
• Excluded from analysis (n = 17)
Excluded from mITT (n = 5)
Met exclusion criterion #2 (n = 1)
Indeterminate DRC clinical response at Day 14 (n = 6)
Indeterminate DRC mycological/ radiological response at Day 14 (n = 8)
Received concomitant antifungal that could confound assessment of global response at Day 14 (n = 3)

Recruitment

The study was conducted between 2018 and 2021 at 66 centres in 15 countries (including 7 EU countries).

Baseline data

The median age (range) was similar between the rezafungin for injection and caspofungin treatment groups (59.5 [19–89] and 62.0 [20–91] years, respectively). The percentages of subjects in each age group were similar between treatments with 60.0% and 58.6% of rezafungin for injection and caspofungin subjects, respectively, in the <65 years age category, and 40.0% and 41.4% in the ≥65 years category, respectively. Males comprised 67.0% and 56.6% of rezafungin for injection and caspofungin subjects, respectively. There was no notable difference observed in demographics and baseline characteristics between the treatment groups.

For rezafungin for injection and caspofungin treatment groups, 70.0% and 68.7%, respectively, had a final diagnosis of candidemia only (the balance were subjects with invasive candidiasis). Blood culture was the most common diagnostic method utilized, for 69.8% of subjects overall.

Most subjects had a modified APACHE II score <20, representing 84.0% and 81.8% of rezafungin for injection and caspofungin subjects, respectively; with ANC at baseline ≥ 500/µL in 88.0% and 93.9%, respectively.

All subjects had at least one *Candida* infection risk factor in the three months prior to screening. The most common (in ≥ 30% of either treatment group) *Candida* risk factors at screening were broad-spectrum antibiotic therapy in 75.3% and 67.0% subjects in the rezafungin for injection and caspofungin treatment groups, respectively, followed by central venous catheter (59.1% and 61.7%, respectively), and major surgery (34.4% and 35.1%, respectively). The percentages of subjects were similar between treatment groups for all *Candida* infection risk factors at screening with the exception of currently mechanically ventilated, with this risk factor occurring in 17.2% and 29.8% of rezafungin for injection and caspofungin subjects, respectively.

There were 69 subjects in each of the rezafungin for injection and caspofungin treatment groups in the mITT Population that had a positive blood culture at screening. Among these, 58 (84.1%) and 52 (75.4%) subjects in the rezafungin for injection and caspofungin treatment groups, respectively, had a catheter in place at screening. There were 7 (12.1%) and 14 (26.9%) subjects in the rezafungin for injection and caspofungin treatment groups, respectively, who had their catheter removed within 48 hours of diagnosis. Median duration of catheter placement of any type since insertion was at 17.00 days in the rezafungin for injection group and 16.00 days in the caspofungin group.

The number of subjects with modified APACHE scores ≥ 20 (15 for rezafungin and 18 for caspofungin) or with ANC < 500/µL (9 for rezafungin and 6 for caspofungin) can be considered limited. The very low percentage of subjects with neutropenia does preclude determination as to whether there may be an advantage conferred by using a higher dose in such patients. Therefore, absence of enough patients with ANC<500 may preclude the approval in the intended indication. If available, additional data regarding clinical efficacy and safety of rezafungin in neutropenic patients (e.g. observational studies, compassionate use) should be provided to support the approval of an indication that includes this population.

Numbers analysed

Two hundred and twenty-two subjects were screened, with 199 subjects randomised. A total of 187 subjects were included in the mITT Population: 93 in the rezafungin group, and 94 in the caspofungin group.

Outcomes and estimation

Primary endpoint

The primary endpoint for the EMA in the Phase 3 ReSTORE study, global response as assessed by the DRC at Day 14 (±1 day) is summarised in the following table for the mITT Population. The rate of subjects with cure was 59.1% and 60.6% in the rezafungin and caspofungin groups, respectively. The failure rate (not including indeterminate responses) was 30.1% and 30.9% in the rezafungin and caspofungin groups, respectively. The indeterminate rate was 10.8% and 8.5%, respectively. The primary reasons for an indeterminate response were lost to follow-up and withdrawal of consent; it is unknown if these were related to COVID-19. Noninferiority of rezafungin was demonstrated (weighted treatment difference of -1.1 [95% CI: -14.9 to 12.7]), with the lower limit of the 95% CI for the difference in the mITT Population exceeding -20%.

The per protocol population was advised in the scientific advices. For a NI objective, the PP is more conservative than the ITT/mITT. No PP analysis has been defined, although analyses from the clinically evaluable population have been provided.
The post-hoc defined PP population in the study included all subjects in the mITT population who met all inclusion and exclusion criteria and received at least 85% of their assigned study medication. There were 89/93 and 89/94 subjects in the rezafungin and caspofungin mITT populations eligible for the PP analysis.

The observed global cure rates at day 14 in the PP population as defined were almost identical for the two treatments, being 59.6% vs. 60.7%, and very similar to those in the mITT population, being 59.1% vs. 60.6%. The calculated lower bound of the 95% CI was -15.4% in both populations. For the global cure at day 5, the comparisons between populations were again very similar, with lower bounds of the 95% CI at -10.5% and -10.1% in the mITT and PP populations, respectively. Thus results for the two populations lead to similar conclusions.

The analyses of other endpoints in the PP population, including ACM at day 30, also give rise to similar conclusions as drawn for the mITT population. The results for the PP population therefore support those reported for the mITT population.

Table 28. ReSTORE Global Cure as Assessed by Data Review Committee at Day 14 (± 1 day) in the mITT and PP Populations

DRC Global Response, n (%)	Rezafungin	Caspofungin	Difference (95% CI)
mITT Population	N = 93	N = 94	
Cure	55 (59.1)	57 (60.6)	-1.5 (-15.4, 12.5)
Failure or Indeterminate	38 (40.9)	37 (39.4)	
Failure	28 (30.1)	29 (30.9)	
Indeterminate	10 (10.8)	8 (8.5)	
PP Population	N = 89	N = 89	
Cure	53 (59.6)	54 (60.7)	-1.1 (-15.4, 13.2)
Failure or Indeterminate	36 (40.4)	35 (39.3)	
Failure	27 (30.3)	27 (30.3)	
Indeterminate	9 (10.1)	8 (9.0)	

CI: Confidence interval; DRC: Data Review Committee; mITT: Modified Intent-to-Treat; N: Number of subjects; n: Number of subjects in the category; PP: Per protocol.
Notes: Unstratified analysis presented. Two-sided 95% CI for the observed differences in cure rates, rezafungin for injection treatment group minus caspofungin treatment group, are calculated using the unadjusted methodology of Miettinen and Nurminen. Percentages were calculated using the total number of subjects in the analysis set.

Although non-inferiority of rezafungin was demonstrated for global response as assessed by the DRC at Day 14 (±1 day) in the mITT Population, the rate of global response as assessed by the DRC at Day 14 (±1 day) was not higher in the rezafungin group than the caspofungin group, and the difference between the treatment groups was therefore not tested for superiority.

A pre-defined subgroup analysis was undertaken in two further populations mITT2 and mITT3, with the intent of assessing the efficacy of rezafungin treatment commenced when subjects have ongoing IC. Analysis of the primary outcome (Global cure at Day 14) for the mITT, mITT2, and mITT3 populations demonstrate that timing of the culture in relation to study drug administration does not significantly impact the results.

Table 22. Global Cure at Day 14 for mITT, mITT2, and mITT3

Endpoint/Population	Rezafungin n/N (%)	Caspofungin n/N (%)	Treatment difference [95% CI]
Global cure at Day 14 (±1 day)			
mITT	55/93 (59.1)	57/94 (60.6)	-1.1 [-14.9, 12.7]
mITT2	21/38 (55.3)	23/46 (50.0)	5.3 [-16.1, 26.0]
mITT3	31/55 (56.4)	33/60 (55.0)	1.4 [-16.7, 19.3]

CI: Confidence interval; mITT: Modified Intent-to-Treat; N: Number of subjects; n: Number of subjects in the category.

The above table shows that in two out of the three populations, NI cannot be concluded. The applicant was asked to compute a probability of NI. That is the probability that the true difference exceeds -20%. This probability should be reasonably high to provide confidence in a NI conclusion. The response provided by the applicant indicates that the probability that the true difference in global cure rates is within -20% in the mITT population is very high (1.00) and the probability that the true difference is within -15% is 0.97. The probability that the observed difference is within -10% is 0.88 in the mITT population. Whilst this response does not address the concern over the calculated confidence intervals, it does suggest that the intervals presented are highly likely to be accurate.

Reasons for failure or indeterminate global response as assessed by the DRC at Day 14 (±1 day) in the Phase 3 ReSTORE study are summarised in the table below for the mITT Population. The number of subjects who were failures was 28 and 29 in the rezafungin and caspofungin groups, respectively. The most common reasons for failure were new therapy and death (which are reasons for failure for both mycological and clinical response).

Table 25. ReSTORE Reasons for Failure or Indeterminate Global Response as Assessed by the DRC at Day 14 (±1 day) (mITT Population)

Reason, n (%)	Rezafungin (N = 93)	Caspofungin (N = 94)
Failure [a]	28	29
For Mycological Response	24	27
Positive blood culture	0	1 (3.4)
Positive culture from normally sterile site	1 (3.6)	1 (3.4)
Clinical failure or lack of improvement in radiographic abnormalities (IC Subjects only)	1 (3.6)	7 (24.1)
New or prolonged therapy	12 (42.9)	9 (31.0)
Subject died	10 (35.7)	9 (31.0)
For Clinical Response	27	27
Progression or recurrence of signs/symptoms of candidemia/IC requiring new or prolonged therapy	2 (7.1)	3 (10.3)
Lack of resolution of signs/symptoms of candidemia/IC requiring new or prolonged therapy	4 (14.3)	7 (24.1)
New or prolonged antifungal therapy (Only allowed at Follow-up visit*)	8 (28.6)	8 (27.6)
Adverse event which requires discontinuation of study drug	3 (10.7)	0
Subject died	10 (35.7)	9 (31.0)
For Radiological Response [b]	2	8
Progression of radiological or other imaging findings of IC	0	1 (3.4)
New radiological or other imaging findings of IC	1 (3.6)	2 (6.9)
Lack of improvement of radiological or other imaging findings of IC	0	4 (13.8)
Subject died	1 (3.6)	1 (3.4)
Indeterminate [c]	10	8
For Mycological Response	9	8
Subject was lost to follow-up	2 (20.0)	2 (25.0)
Subject withdrew consent	3 (30.0)	3 (37.5)
Blood specimen/result not available	1 (10.0)	1 (12.5)
Sterile site specimen/result and Clinical/radiographic assessments not available (IC subjects only)	1 (10.0)	1 (12.5)
Extenuating circumstances	2 (20.0)	1 (12.5)
For Clinical Response	7	6
Subject was lost to follow-up	2 (20.0)	2 (25.0)
Subject withdrew consent	3 (30.0)	3 (37.5)
Subject missed study visit	1 (10.0)	1 (12.5)
Extenuating circumstances	1 (10.0)	0
For Radiological Response [b]	5	2
Subject was lost to follow-up	1 (10.0)	0
Subject withdrew consent	2 (20.0)	1 (12.5)
Radiology or other imaging not completed	2 (20.0)	1 (12.5)
Extenuating circumstance	0	0

CI: Confidence interval; DRC: Data Review Committee; IC: Invasive candidiasis; mITT: Modified Intent-to-Treat; N: Number of subjects; n: Number of subjects in the category.

Secondary endpoints

1) All-Cause Mortality at Day 30

The rate of subjects who were either known to be deceased or with unknown survival status was 23.7% and 21.3% in the rezafungin and caspofungin groups, respectively. All attempts were made to obtain survival data including for those subjects who discontinued the study prior to Day 30. The rate of unknown survival status was low and the same in both treatment arms (3.2%). These subjects are reported as discontinuing the study early due to lost to follow-up or withdrawal of consent; it is unknown if these were related to COVID-19. Non-inferiority of rezafungin was demonstrated (treatment difference of 2.4 [95% CI: -9.7 to 14.4]), with the upper limit of the 95% CI for the difference in the mITT Population lower than 20%. A total of 20.4% and 18.1% of subjects in the rezafungin and caspofungin groups were known to be deceased.

Given that that ACM at Day 30 was higher in the rezafungin group compared with the caspofungin group, the difference was not tested for superiority.

Table 26. ReSTORE All-Cause Mortality at Day 30 (mITT Population)

Characteristic, n (%)	Rezafungin (N = 93)	Caspofungin (N = 94)	Difference (95% CI)
Deceased [a]	22 (23.7)	20 (21.3)	2.4 (-9.7, 14.4)
Known deceased	19 (20.4)	17 (18.1)	
Unknown survival status	3 (3.2)	3 (3.2)	
Alive	71 (76.3)	74 (78.7)	

CI: Confidence interval; mITT: Modified Intent-to-Treat; N: Number of subjects; n: Number of subjects in the category.
Subjects who died on or before Day 30, or with unknown survival status.
Notes: Two-sided 95% confidence interval (CI) for the observed difference in death rates, rezafungin treatment group minus caspofungin treatment group, was calculated using the unadjusted methodology of Miettinen and Nurminen. Percentages were calculated using the total number of subjects in the mITT population in each treatment group as the denominator.
Source: Phase 3 ReSTORE CSR, 5.3.5.1 CD101.IV.3.05, Table 14.2.1.1

2) Global cure at Day 5, Day 30, EOT and FU

Global response in the Phase 3 ReSTORE study as assessed by the DRC was analysed by visit and summarised in the table below for the mITT Population. At each of the secondary endpoint visits, Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59), the response rates were similar between treatment groups. Response rates were low after Day 14 due to the increase in the failure rate and/or the indeterminate rate.

Table 28. ReSTORE Global Response as Assessed by Data Review Committee by Visit (mITT Population)

Visit, n (%)	DRC Global Response	Rezafungin (N = 93)	Caspofungin (N = 94)	% Difference (95% CI)
Day 5	Cure	52 (55.9)	49 (52.1)	3.8 (-10.5, 17.9)
	Failure or Indeterminate	41 (44.1)	45 (47.9)	
	Failure	32 (34.4)	37 (39.4)	
	Indeterminate	9 (9.7)	8 (8.5)	
Day 14 (±1 day)	Cure	55 (59.1)	57 (60.6)	-1.5 (-15.4, 12.5)
	Failure or Indeterminate	38 (40.9)	37 (39.4)	
	Failure	28 (30.1)	29 (30.9)	
	Indeterminate	10 (10.8)	8 (8.5)	
Day 30 (-2 days)	Cure	46 (49.5)	46 (48.9)	0.5 (-13.7, 14.7)
	Failure or Indeterminate	47 (50.5)	48 (51.1)	
	Failure	31 (33.3)	36 (38.3)	
	Indeterminate	16 (17.2)	12 (12.8)	
EOT (≤2 days of last dose)	Cure	56 (60.2)	59 (62.8)	-2.6 (-16.4, 11.4)
	Failure or Indeterminate	37 (39.8)	35 (37.2)	
	Failure	29 (31.2)	32 (34.0)	
	Indeterminate	8 (8.6)	3 (3.2)	
Follow-up (Days 52–59)	Cure	42 (45.2)	39 (41.5)	3.7 (-10.5, 17.7)
	Failure or Indeterminate	51 (54.8)	55 (58.5)	
	Failure	38 (40.9)	42 (44.7)	
	Indeterminate	13 (14.0)	13 (13.8)	

CI: Confidence interval; DRC: Data Review Committee; EOT: End of treatment; mITT: Modified Intent-to-Treat; N: Number of subjects; n: Number of subjects in the category.

Notes: Two-sided 95% confidence intervals (CIs) for the observed differences in cure rates (rezafungin treatment group minus caspofungin treatment group) were calculated using the unadjusted methodology of Miettinen and Nurminen. Percentages were calculated using the total number of subjects in the mITT Population in each treatment group as the denominator.

Source: Phase 3 ReSTORE CSR, 5.3.5.1, CD101.IV.3.05, Table 14.2.3.3

3) Mycological Eradication by Visit

Mycological response by visit in the Phase 3 ReSTORE study is summarised in the table below for the mITT Population. At each of the visits, Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59), eradication rates were similar between treatment groups.

Table 29. ReSTORE Mycological Response by Visit (mITT Population)

Visit, n (%)	Mycological Response	Rezafungin (N = 93)	Caspofungin (N = 94)	Difference (95% CI)
Day 5	Eradication	64 (68.8)	58 (61.7)	7.1 (-6.6, 20.6)
	Failure or Indeterminate	29 (31.2)	36 (38.3)	
	Failure	25 (26.9)	27 (28.7)	
	Indeterminate	4 (4.3)	9 (9.6)	
Day 14 (±1 day)	Eradication	63 (67.7)	62 (66.0)	1.8 (-11.7, 15.2)
	Failure or Indeterminate	30 (32.3)	32 (34.0)	
	Failure	26 (28.0)	28 (29.8)	
	Indeterminate	4 (4.3)	4 (4.3)	
Day 30 (-2 day)	Eradication	56 (60.2)	53 (56.4)	3.8 (-10.3, 17.8)
	Failure or Indeterminate	37 (39.8)	41 (43.6)	
	Failure	33 (35.5)	38 (40.4)	
	Indeterminate	4 (4.3)	3 (3.2)	
EOT (≤2 days of last dose)	Eradication	63 (67.7)	63 (67.0)	0.7 (-12.7, 14.1)
	Failure or Indeterminate	30 (32.3)	31 (33.0)	
	Failure	26 (28.0)	29 (30.9)	
	Indeterminate	4 (4.3)	2 (2.1)	
Follow-up (Days 52–59)	Eradication	48 (51.6)	49 (52.1)	-0.5 (-14.7, 13.7)
	Failure or Indeterminate	45 (48.4)	45 (47.9)	
	Failure	41 (44.1)	43 (45.7)	
	Indeterminate	4 (4.3)	2 (2.1)	

CI: Confidence interval; EOT: End of treatment; mITT: Modified Intent-to-Treat; N: Number of subjects; n: Number of subjects in the category.

Notes: Eradication includes both documented and presumed eradication. Two-sided 95% confidence intervals (CIs) for the observed differences in eradication rates (rezafungin treatment group minus caspofungin treatment group) were calculated using the unadjusted methodology of Miettinen and Nurminen. Percentages were calculated using the total number of subjects in the mITT Population in each treatment group as the denominator.
Source: Phase 3 ReSTORE CSR, 5.3.5.1, CD101.IV.3.05, Table 14.2.4.1.

4) Investigators' Assessment of Clinical Response by Visit

Investigators' assessment of clinical response by visit in the Phase 3 ReSTORE study is summarised in the table below for the mITT Population. The clinical response rate for rezafungin was numerically lower compared to caspofungin at Day 5 (63.4% versus 74.5%, respectively), and was similar at all other visits.

Table 31. ReSTORE Investigators' Assessment of Clinical Response by Visit (mITT Population)

Visit, n (%)	Clinical Response	Rezafungin (N = 93)	Caspofungin (N = 94)	Difference (95% CI)
Day 5	Cure	59 (63.4)	70 (74.5)	-11.0 (-24.0, 2.3)
	Failure or Indeterminate	34 (36.6)	24 (25.5)	
	Failure	31 (33.3)	22 (23.4)	
	Indeterminate	3 (3.2)	2 (2.1)	
Day 14 (±1 day)	Cure	62 (66.7)	63 (67.0)	-0.4 (-13.8, 13.1)
	Failure or Indeterminate	31 (33.3)	31 (33.0)	
	Failure	26 (28.0)	27 (28.7)	
	Indeterminate	5 (5.4)	4 (4.3)	
Day 30 (-2 days)	Cure	51 (54.8)	52 (55.3)	-0.5 (-14.6, 13.7)
	Failure or Indeterminate	42 (45.2)	42 (44.7)	
	Failure	32 (34.4)	34 (36.2)	
	Indeterminate	10 (10.8)	8 (8.5)	
EOT (≤2 days of last dose)	Cure	65 (69.9)	64 (68.1)	1.8 (-11.5, 15.0)
	Failure or Indeterminate	28 (30.1)	30 (31.9)	
	Failure	22 (23.7)	26 (27.7)	
	Indeterminate	6 (6.5)	4 (4.3)	
Follow-up (Days 52–59)	Cure	46 (49.5)	44 (46.8)	2.7 (-11.6, 16.8)
	Failure or Indeterminate	47 (50.5)	50 (53.2)	
	Failure	38 (40.9)	40 (42.6)	
	Indeterminate	9 (9.7)	10 (10.6)	

CI: Confidence interval; EOT: End of treatment; mITT: Modified Intent to-Treat; N: Number of subjects; n: Number of subjects in the category.
Notes: Two-sided 95% confidence intervals (CIs) for the observed differences in cure rates (rezafungin treatment group minus caspofungin treatment group) were calculated using the unadjusted methodology of Miettinen and Nurminen. Percentages were calculated using the total number of subjects in the mITT Population in each treatment group as the denominator.
Source: Phase 3 ReSTORE CSR, 5.3.5.1, CD101.IV.3.05, Table 14.2.6.1

5) Radiological Response by Investigator by Visit

The small sample size of subjects with a radiological response by Investigator resulted in large 95% CIs, making comparison between treatment groups and between subgroups less reliable.

Exploratory endpoint

Resolution of systemic signs and symptoms attributable to candidemia and/or IC by visit in the Phase 3 ReSTORE study is summarised in the table below for the mITT Population. Resolution of attributable signs or symptoms was high and similar between treatment groups at all visits (although no data is included for subjects who died prior to the noted visit[s], and they are therefore excluded from this analysis). At Day 14, mycological eradication and resolution of attributable signs and symptoms was 88.4% in the rezafungin group compared to 70.7% in the caspofungin group; and 82.1% and 70.3%, respectively, at Day 30. Resolution of attributable signs or symptoms alone was also higher at Day 14 for rezafungin (98.6%) compared to caspofungin (88.0%).

Table 32. ReSTORE Resolution of Systemic Signs and Symptoms Attributable to Candidemia and/or Invasive Candidiasis by Visit (mITT Population)

Category Visit, n (%)	Rezafungin (N = 93)	Caspofungin (N = 94)
Number of subjects with at least one attributable sign or symptom at screening [a]	93/ 93 (100.0)	94/ 94 (100.0)
Resolution of attributable signs or symptoms [b]		
Day 5	64/ 81 (79.0)	69/ 85 (81.2)
Day 14 (±1 day)	68/ 69 (98.6)	66/ 75 (88.0)
Day 30 (-2 days)	56/ 56 (100.0)	60/ 64 (93.8)
Follow-up (Days 52–59)	53/ 54 (98.1)	52/ 56 (92.9)
Mycological eradication and resolution of attributable signs or symptoms [b]		
Day 5	53/ 81 (65.4)	53/ 85 (62.4)
Day 14 (±1 day)	61/ 69 (88.4)	53/ 75 (70.7)
Day 30 (-2 days)	46/ 56 (82.1)	45/ 64 (70.3)
Follow-up (Days 52–59)	41/ 54 (75.9)	39/ 56 (69.6)

mITT: Modified Intent to-Treat; N: Number of subjects; n: Number of subjects in the category.

a. Percentages were calculated as the number of subjects with at least one attributable sign or symptom at screening divided by the number of subjects with a non-missing assessment of systemic signs at screening in the mITT population.
b. Percentages were calculated as the number of subjects with resolution of all attributable systemic signs of candidemia and/or invasive candidiasis that were present at screening divided by the number of subjects with at least one attributable sign or symptom at screening and a non-missing assessment of systemic signs at the respective visit.

Source: Phase 3 ReSTORE CSR, 5.3.5.1 CD101.IV.3.05, Table 14.2.7

Exploratory analysis

The percentage of subjects with negative blood culture was 89.9% and 81.2% in the rezafungin and caspofungin groups respectively, with median time to first negative blood culture of 23.9 hours and 27.0 hours, respectively, which was not statistically significant (P=0.175).

At 24 hours, the percentage of subjects with negative blood culture was 53.7% and 46.2% in the rezafungin and caspofungin groups, respectively; at 48 hours, the rate of subjects with negative blood culture was 74.2% and 64.1% in the rezafungin and caspofungin groups, respectively.

Median values of total number of hospital days, total number of days in the ICU across all admissions, and total number of days in the General Ward across all admissions were similar between treatment groups.

Admissions to hospital and ICU in the Phase 3 ReSTORE study are summarised in the table below for the mITT Population. New admissions to the ICU since Day 1 occurred in 12.9% versus 7.4% of rezafungin and caspofungin subjects, respectively. The median total number of days in the hospital across all admissions was 21.0 days and 24.0 days, respectively. Of note, the median total number of days in the ICU across all admissions was 5.0 days in the rezafungin compared to 14.5 days in the caspofungin group, and the median longest length of ICU stay was 5.0 days versus 13.0 days, respectively.

Table 33. ReSTORE Admissions to Hospital and Intensive Care Unit (mITT Population)

Category, n (%)	Rezafungin (N = 93)	Caspofungin (N = 94)
Number of subjects newly admitted to ICU since Day 1 [a]	12 (12.9)	7 (7.4)
Number of ICU admissions per subject [b]		
One admission only	11 (91.7)	6 (85.7)
Two admissions	1 (8.3)	1 (14.3)
Total number of days in hospital across all admissions [c]		
n	70	75
Mean	25.8	27.1
SD	19.44	17.61
Median	21.0	24.0
25th–75th percentile	9.0–51.0	12.0–40.0
Min, Max	2, 59	1, 59
Total number of days in ICU across all admissions [d]		
n	17	28
Mean	13.9	23.1
SD	18.34	19.90
Median	5.0	14.5
25th–75th percentile	2.0–16.0	5.5–41.5
Min, Max	1, 58	2, 57
Total number of days in General Ward across all admissions [c]		
n	68	66
Mean	23.1	21.6
SD	18.16	15.94
Median	17.5	16.0
25th–75th percentile	8.0–35.5	9.0–31.0
Min, Max	1, 59	1, 59
Longest length of each hospital stay (days) [c]		
n	70	75
Mean	24.2	25.9
SD	19.27	17.81
Median	17.0	22.0
25th–75th percentile	8.0–40.0	11.0–38.0
Min, Max	2, 59	3, 59

Category, n (%)	Rezafungin (N = 93)	Caspofungin (N = 94)
Longest length of ICU stay (days) [d]		
n	17	28
Mean	11.8	22.9
SD	15.21	19.99
Median	5.0	13.0
25th–75th percentile	2.0–11.0	5.5–41.5
Min, Max	1, 54	2, 57

ICU: Intensive care unit; Max: Maximum; Min: Minimum; mITT: Modified Intent to-Treat; N: Number of subjects; n: Number of subjects in the category; SD: Standard deviation.
a. Admitted due to the underlying disease on or after Study Day 1.
b. Percentages were calculated using the number of subjects with an admission in the mITT Population in each treatment group as the denominator.
c. Subjects who died during hospitalisation were not included in the summary.
d. Subjects who died during ICU stay were not included in the summary.

Source: Phase 3 ReSTORE CSR, 5.3.5.1, CD101.IV.3.05, Table 14.2.9.1

Global response as assessed by the DRC at Day 14 (±1 day) is summarised in the table below for the mITT Population. For those species with sufficient numbers to enable comparison, the response rates for *C. glabrata, C. tropicalis*, and *C. parapsilosis* were higher in the rezafungin group (66.7%, 70.0%, and 75.0%, respectively) compared to the caspofungin group (56.0%, 58.8%, and 64.7%, respectively).

Table 35. ReSTORE Global Response as Assessed by the DRC at Day 14 (±1 day) by Baseline *Candida* Species (mITT Population)

Candida Species at Baseline, n/N1 (%)	Rezafungin (N=93)	Caspofungin (N=94)
Candida albicans	21/39 (53.8)	23/40 (57.5)
Candida glabrata	16/24 (66.7)	14/25 (56.0)
Candida tropicalis	14/20 (70.0)	10/17 (58.8)
Candida parapsilosis	6/8 (75.0)	11/17 (64.7)
Candida dubliniensis	2/3 (66.7)	1/1 (100.0)
Candida krusei	0/2 (0.0)	2/2 (100.0)
Candida guilliermondii	1/2 (50.0)	0
Candida lusitaniae	1/1 (100.0)	1/1 (100.0)
Candida metapsilosis	1/1 (100.0)	0
Candida nivariensis	0	1/1 (100.0)

N: Number of subjects in the mITT Population; n: Number of subjects with DRC global response of Cure at Day 14; N1: Number of subjects in the mITT Population with the specified *Candida* pathogen at Baseline.

Source: Phase 3 ReSTORE CSR, 5.3.5.1, CD101.IV.3.05, Table 14.2.3.17

Investigators' assessment of clinical response of cure at Day 14 (±1 day) is summarised in the table below for the mITT Population. For those species with sufficient numbers to enable comparison, the response rates for were generally similar, although the response rate for *C. tropicalis* was higher in the rezafungin group (75.0%) compared to the caspofungin group (52.9%).

Mycological response by visit and final diagnosis in the Phase 3 ReSTORE study is summarised in the table below for the mITT Population. For each final diagnosis (candidemia only and IC) at each of the visits, Day 5, Day 14, Day 30, EOT, and Follow-up, eradication rates were generally similar between treatment groups, with the exception of the subjects with final diagnosis of candidemia only where rezafungin was higher

compared to caspofungin at Day 5 (78.1% versus 68.7%, respectively), and the subjects with final diagnosis of IC at Day 30 (55.2% versus 48.1%, respectively) and Follow-up (51.7% versus 40.7%, respectively).

Table 38. ReSTORE Mycological Response (Programmatically Derived) by Visit and Final Diagnosis (mITT Population)

Visit, n (%)	Mycological Response	Rezafungin	Caspofungin	Difference (95% CI)
Candidemia Only		**(n = 64)**	**(n = 67)**	
Day 5	Eradication	50 (78.1)	46 (68.7)	9.5 (-5.8, 24.4)
	Failure or Indeterminate	14 (21.9)	21 (31.3)	
	Failure	13 (20.3)	17 (25.4)	
	Indeterminate	1 (1.6)	4 (6.0)	
Day 14 (±1 day)	Eradication	46 (71.9)	47 (70.1)	1.7 (-13.9, 17.2)
	Failure or Indeterminate	18 (28.1)	20 (29.9)	
	Failure	17 (26.6)	18 (26.9)	
	Indeterminate	1 (1.6)	2 (3.0)	
Day 30 (-2 day)	Eradication	40 (62.5)	40 (59.7)	2.8 (-13.9, 19.3)
	Failure or Indeterminate	24 (37.5)	27 (40.3)	
	Failure	23 (35.9)	25 (37.3)	
	Indeterminate	1 (1.6)	2 (3.0)	
EOT (≤2 days of last dose)	Eradication	46 (71.9)	47 (70.1)	1.7 (-13.9, 17.2)
	Failure or Indeterminate	18 (28.1)	20 (29.9)	
	Failure	17 (26.6)	18 (26.9)	
	Indeterminate	1 (1.6)	2 (3.0)	
Follow-up (Days 52–59)	Eradication	33 (51.6)	38 (56.7)	-5.2 (-21.9, 11.9)
	Failure or Indeterminate	31 (48.4)	29 (43.3)	
	Failure	30 (46.9)	28 (41.8)	
	Indeterminate	1 (1.6)	1 (1.5)	
Invasive Candidiasis		**(n = 29)**	**(n = 27)**	
Day 5	Eradication	14 (48.3)	12 (44.4)	3.8 (-21.9, 29.0)
	Failure or Indeterminate	15 (51.7)	15 (55.6)	
	Failure	12 (41.4)	10 (37.0)	
	Indeterminate	3 (10.3)	5 (18.5)	

Visit, n (%)	Mycological Response	Rezafungin	Caspofungin	Difference (95% CI)
Day 14 (±1 day)	Eradication	17 (58.6)	15 (55.6)	3.1 (-22.4, 28.3)
	Failure or Indeterminate	12 (41.4)	12 (44.4)	
	Failure	9 (31.0)	10 (37.0)	
	Indeterminate	3 (10.3)	2 (7.4)	
Day 30 (-2 day)	Eradication	16 (55.2)	13 (48.1)	7.0 (-18.9, 32.1)
	Failure or Indeterminate	13 (44.8)	14 (51.9)	
	Failure	10 (34.5)	13 (48.1)	
	Indeterminate	3 (10.3)	1 (3.7)	
EOT (≤2 days of last dose)	Eradication	17 (58.6)	16 (59.3)	-0.6 (-25.8, 24.7)
	Failure or Indeterminate	12 (41.4)	11 (40.7)	
	Failure	9 (31.0)	11 (40.7)	
	Indeterminate	3 (10.3)	0	
Follow-up (Days 52–59)	Eradication	15 (51.7)	11 (40.7)	11.0 (-15.1, 35.6)
	Failure or Indeterminate	14 (48.3)	16 (59.3)	
	Failure	11 (37.9)	15 (55.6)	
	Indeterminate	3 (10.3)	1 (3.7)	

CI: Confidence interval; EOT: End of treatment; mITT: Modified Intent-to-Treat; N: Number of subjects; n: Number of subjects in the category.

Notes: Eradication includes both documented and presumed eradication. Two-sided 95% confidence intervals (CIs) for the observed differences in eradication rates (rezafungin treatment group minus caspofungin treatment group) were calculated using the unadjusted methodology of Miettinen and Nurminen. Percentages were calculated using the total number of subjects in the mITT Population in each treatment group as the denominator.

Source: Phase 3 ReSTORE CSR, 5.3.5.1, CD101.IV.3.05, Table 14.2.4.3

For each diagnosis at screening (candidemia only and IC) at each of the visits, Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59), eradication rates were generally similar between treatment groups, with the exception of the subjects with diagnosis at screening of IC where Day 30 was 57.7% for rezafungin versus 48.1% for caspofungin, and Follow-up was 57.7% versus 40.7%, respectively.

The analysis of the primary outcome for the two other analysed populations (mITT2 and mITT3) suggests that patients with confirmation of infection nearer to the time of randomisation would have the same benefit if treated with either product. These populations are however smaller than the mITT population not allowing for an adequate assessment of the observed differences.

- **Ancillary analyses**

A sensitivity analysis was performed in the Clinical Evaluation Population. Non-inferiority of rezafungin was again demonstrated (weighted treatment difference of 1.1 [95% CI: -13.3 to 15.1]), with the lower limit of the 95% CI for the difference in the mITT Population exceeding -20%.

Table 24. ReSTORE Sensitivity Analysis of Global Response as Assessed by Data Review Committee at Day 14 (±1 day) (CE Population)

DRC Global Response, n (%)	Rezafungin (N = 77)	Caspofungin (N = 82)	Difference (95% CI)
Cure	53 (68.8)	55 (67.1)	1.1 (-13.3, 15.1)
Failure or Indeterminate	24 (31.2)	27 (32.9)	
Failure	24 (31.2)	27 (32.9)	
Indeterminate	0	0	

ANC: Absolute neutrophil count; APACHE II: Acute Physiology and Chronic Health Evaluation; CE: Clinically Evaluable; CI: Confidence interval; DRC: Data Review Committee; mITT: Modified Intent-to-Treat; N: Number of subjects; n: Number of subjects in the category.
Notes: Two-sided 95% confidence intervals (CIs) for the weighted differences in cure rates (rezafungin treatment group minus caspofungin treatment group) were calculated adjusting for the two randomisation strata (diagnosis (candidemia only; invasive candidiasis) and APACHE II score/ANC (APACHE II score ≥20 OR ANC <500 cells/µL; APACHE II score <20 AND ANC ≥500 cells/µL) at screening) using methodology of Miettinen and Nurminen. Cochran-Mantel-Haenszel weights were used for the stratum weights. Percentages were calculated using the total number of subjects in the CE Population in each treatment group as the denominator.
Source: Phase 3 ReSTORE CSR, 5.3.5.1, CD101.IV.3.05, Table 14.2.3.5

P*ost-hoc* subgroup analyses were also performed to assess the impact of timing of sampling for culture in relation to study drug administration on mycological eradication rates (the component of the composite primary endpoint that focuses on the fungicidal activity of the study drugs). In both the mITT2 and mITT3 populations the data indicate that rezafungin consistently improved the clearance of *Candida* in patients with active infection compared with caspofungin, particularly in the days following study drug administration (see table below).

In the mITT2 population (subjects meeting the most stringent definition of positive cultures proximal to randomisation), the rate of mycological eradication at Day 5 was >20% higher in the rezafungin arm compared with caspofungin with a 95% CI of (-0.2, 40.2). A marked difference was still observed in the mITT3 population when cultures from sterile sites was pushed out to 96 hours prior to randomisation, with a difference (95% CI) of 11.1% (-7.2, 28.7) observed in favour of rezafungin.

Additionally, rezafungin showed clear benefits when subjects were analysed by status according to administration of systemic antifungals in the 48 hours preceding randomisation. In subjects who had not received prior therapy, and thus were more likely to have an active infection, mycological eradication rates (95% CI) were 19.2% (-9.4, 43.0) higher in those who received rezafungin compared with caspofungin-treated subjects.

By Day 14, the differences in mycological eradication between rezafungin and caspofungin become less marked, irrespective of when the culture is taken in relation to study drug administration with differences (95% CI) of 1.8% (-12.1, 15.6), 8.8% (-12.4, 29.0), and 2.8% (-15.2, 20.5) in favour of rezafungin for mITT, mITT2, and mITT3 populations respectively. However, the impact of antifungal therapy prior to randomisation continued to show a clear benefit for rezafungin-treated subjects, with a mycological eradication rate (95% CI) 17.8% (-9.6, 40.5) higher than caspofungin-treated subjects.

Table 30. Mycological Eradication at Day 5 and Day 14 as Assessed by DRC (mITT, mITT2, mITT3)

Population	Mycological Eradication		
	Rezafungin n/N (%) [95% CI]	Caspofungin n/N (%) [95% CI]	Difference (C-R) (95% CI)
Day 5			
mITT	63/91 (69.2%) [58.7, 78.5]	57/93 (61.3%) [50.6, 71.2]	7.9 (-5.9, 21.5)
mITT2	27/38 (71.1%) [54.1, 84.6]	23/46 (50.0%) [34.9, 65.1]	21.1 (-0.2, 40.2)
mITT3	33/54 (61.1%) [46.9, 74.1]	30/60 (50.0%) [36.8, 63.2]	11.1 (-7.2, 28.7)
Prior Anti-Fungal Therapy (within 2 days of first dose)	49/73 (67.1%) [55.1, 77.7]	40/64 (62.5%) [49.5, 74.3]	4.6 (-11.3, 20.5)
No Prior Anti-Fungal Therapy (within 2 days of first dose)	14/18 (77.8%) [52.4, 93.6]	17/29 (58.6%) [38.9, 76.5]	19.2 (-9.4, 43.0)
Day 14			
mITT	59/92 (64.1%) [53.5, 73.9]	58/93 (62.4%) [51.7, 72.2]	1.8 (-12.1, 15.6)
mITT2	24/38 (63.2%) [46.0, 78.2]	25/46 (54.3%) [39.0, 69.1]	8.8 (-12.4, 29.0)
mITT3	33/54 (61.1%) [46.9, 74.1]	35/60 (58.3%) [44.9, 70.9]	2.8 (-15.2, 20.5)
Prior Anti-Fungal Therapy (within 2 days of first dose)	44/74 (59.5%) [47.4, 70.7]	39/64 (60.9%) [47.9, 72.9]	-1.5 (-17.6, 14.9)
No Prior Anti-Fungal Therapy (within 2 days of first dose)	15/18 (83.3%) [58.6, 96.4]	19/29 (65.5%) [45.7, 82.1]	17.8 (-9.6, 40.5)

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of efficacy for trial STRIVE

Title: A Phase 2, Multicenter, Randomized, Double-blind Study of the Safety, Tolerability, and Efficacy of Intravenous CD101 versus Intravenous Caspofungin Followed by Oral Fluconazole Step-Down in the Treatment of Subjects with Candidemia and/or Invasive Candidiasis		
Study identifier	Protocol Number: CD101.IV.2.03 EudraCT Number: 2015-005599-51 Clinicaltrials.gov Number: NCT02734862	
Design	Multicentre, randomised, prospective, double-blind, two-part study.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 July 2016 – 18 April 2019 not applicable not applicable

Hypothesis	Exploratory study not powered for inferential statistical analyses. A sufficient number of subjects were randomised in Part A to provide substantive analysis of safety, tolerability, and estimate efficacy.		
Treatments groups	Group 1	Rezafungin: 400 mg Day 1 and Day 8; optional for all subjects 400 mg on Day 15, optional for subjects with IC only 400 mg on Day 22. All subjects received treatment through Day 14, optional additional treatment available to Day 15 (all patients) or Day 22 (patients with IC). 81 patients randomised.	
	Group 2	Rezafungin: 400 mg Day 1, 200 mg Day 8; optional for all subjects 200 mg on Day 15, optional for subjects with IC only 200 mg on Day 22. All subjects received treatment through Day 14, optional additional treatment available to Day 15 (all patients) or Day 22 (patients with IC). 57 patients randomised.	
	Caspofungin	Caspofungin IV: 70 mg Day 1, 50 mg/day for 14 days, optional 50 mg/day Days 15-21, optional 50 mg/day Days 22-28 for subjects with IC. After ≥ 3 infusions, a switch to oral step-down treatment was available (fluconazole, 800 mg on first day, 400 mg/day thereafter). All subjects received treatment through Day 14, optional additional treatment available on Days 15-21 (all patients) or Days 22-28 (patients with IC). 69 patients randomised.	
Endpoints and definitions	Co-Primary Endpoint	Overall Success at Day 14	Overall Success (mycological eradication and resolution of systemic signs attributable to candidemia and/or IC) of rezafungin in subjects with
	Secondary	Overall Success Day 5, 28 and Follow-up	Overall Success at Day 5, Day 28 (only for subjects with IC), and Follow-up (FU; Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC, with or without candidemia) in the mITT Population
	Secondary	Mycological Success	Mycological Success (eradication) of rezafungin at Day 5, Day 14, Day 28 (subjects with IC), and FU in the mITT Population
	Secondary	Clinical Cure	Clinical cure as assessed by the Investigator for rezafungin at Day 14, Day 28 (subjects with IC), and FU in the mITT Population
Database lock	16 July 2019 (Part A and B)		

Results and Analysis				
Analysis description	**Primary Analysis – Overall Success at Day 14**			
Analysis population and time point description	Microbiological Intent-to-treat (mITT): All subjects randomised to treatment and received any amount of study drug, with documented Candida infection based on a Central Laboratory (CL) evaluation of an isolate from a blood culture obtained within 96 hours of randomisation or from a specimen obtained from a normally sterile site. Day 14			
Descriptive statistics and estimate variability	Treatment group	Group 1	Group 2	Caspofungin
	Number of subjects	76	46	61
	Overall Success Day 14 n (%)	46 (60.5)	35 (76.1)	41 (67.2)
	95% CI	48.6, 71.6	61.2, 87.4	54.0, 78.7
	Failure/Indeterminate n(%)	30 (39.5)	11 (23.9)	20 (32.8)
	Failure n(%)	20 (26.3)	8 (17.4)	17 (27.9)
	Indeterminate n (%)	10 (13.2)	3 (6.5)	3 (4.9)
Effect estimate per comparison	Primary endpoint	Comparison groups	N/A	
		test statistic	N/A	
		variability statistic	N/A	
		P-value	N/A	
Notes	Success rates were high in all treatment groups with rates of 76.1% in Group 2, 60.5%in Group 1, and 67.2% caspofungin. However, the rate of indeterminate response in Group 1 (13.2%) was more than double that of Group 2 (6.5%) or caspofungin (4.9%), contributing to the comparatively lower rate of success in Group 1. The failure rates were 17.4%, 26.3% and 27.9% for Group 2, Group 1, and caspofungin, respectively. The most common reason for failure in all groups was mycological failure, and the rate of failure attributed to mycological failure was 21.3% in the caspofungin group, 15.8% in Group 1 and 13.0% in Group 2. The reasons for an indeterminate response were considered unrelated to the study drug. These results were similar when data were analysed by diagnosis of candidemia only or IC with the Group 2 having the highest success rates.			

Analysis description	**Pre-Specified Secondary Analysis - Overall Success at Day 5 and Follow-Up**			
Analysis population and time point description	mITT Day 5, Day 28 and Follow-up (Days 45-52 for subjects with candidemia only or Days 52-59 for subjects with IC with/without candidemia)			
Descriptive statistics and estimate variability	Treatment Group	Group 1	Group 2	Caspofungin
	Number of Subjects	76	46	61
	Overall Success at Day 5 n (%)	42 (55.3)	34 (73.9)	34 (55.7)
	95% CI	43.4, 66.7	58.9, 85.7	42.4, 68.5
	Failure/Indeterminate n(%)	34 (44.7)	12 (26.1)	27 (44.3)
	Failure n(%)	24 (31.6)	10 (21.7)	24 (39.3)
	Indeterminate n (%)	10 (13.2)	2 (4.3)	3 (4.9)
	Overall Success at Follow up n(%)	36 (47.4)	30 (65.2)	36 (59.0)
	95% CI	35.8, 59.2	49.8, 78.5	45.7, 71.4
	Failure/Indeterminate n(%)	40 (52.6)	16 (34.8)	25 (41.0)
	Failure n(%)	27 (35.5)	12 (26.1)	23 (37.7)
	Indeterminate n (%)	13 (17.1)	4 (8.7)	2 (3.3)
Notes	Failure rates in the rezafungin groups were lower than caspofungin at the Day 5 and Follow-up Visits.			

Analysis description	**Pre-Specified Secondary Analysis - Mycological Success**				
Analysis population and time point description	mITT Day 5, Day 14, Day 28 (subjects with IC), and FU				
Descriptive statistics and estimate variability	Treatment Group		Group 1	Group 2	Caspofungin
	Number of Subjects		76	46	61
	Day 5	Mycological Success n (%)	50 (65.8)	35 (76.1)	38 (62.3)
		95% CI	54.0, 76.3	61.2, 87.4	49.0, 74.4
		Failure/Indeterminate n (%)	26 (34.2)	11 (23.9)	23 (37.7)
		Failure n (%)	17 (22.4)	9 (19.6)	21 (34.4)
		Indeterminate n (%)	9 (11.8)	2 (4.3)	2 (3.3)
	Day 14	Mycological Success n (%)	50 (65.8)	35 (76.1)	42 (68.9)
		95% CI	54.0, 76.3	61.2, 87.4	55.7, 80.1
		Failure/Indeterminate n (%)	26 (34.2)	11 (23.9)	19 (31.1)
		Failure n (%)	19 (25.0)	8 (17.4)	17 (27.9)
		Indeterminate n (%)	7 (9.2)	3 (6.5)	2 (3.3)
Notes	At Day 5, the rate of indeterminate mycological response in Group 1 (11.8%) was more than double that of Group 2 (4.3%) and caspofungin (3.3%). Failure rate was higher in the caspofungin group (34.4%) compared with Group 2 (19.6%) and Group 1 (22.4%). Mycological success (eradication) rates were highest in Group 2 compared with other groups at Day 5, Day 14, and at the Follow-up Visit. Similarly, at Day 5 in subjects with candidemia only, the rate of indeterminate mycological response in Group 1 (10.5%) was higher than that of Group 2 (5.6%) and caspofungin (4.2%). Failure rate was higher in the caspofungin group (37.5%) compared with Group 1 (17.5%) and Group 2 (19.4%). At Day 14, the rate of indeterminate mycological response in Group 1 (9.2%) was higher than that of Group 2 (6.5%) and caspofungin (3.3%). Failure rate was higher in the caspofungin group (27.9%) compared with Group 2 (17.4%) and Group 1 (25.0%). In subjects with candidemia only, at Day 14 the rate of indeterminate mycological response and the rate of mycological success were more similar across groups. No clear trend was apparent in mycological response by APACHE II Score category.				

Analysis description	**Pre-Specified Secondary Analysis – Clinical Cure**				
Analysis population and time point description	mITT Day 14, Day 28 (subjects with IC), and FU				
Descriptive statistics and estimate variability	Treatment Group		Group 1	Group 2	Caspofungin
	Number of Subjects		76	46	61
	Day 14	Clinical Cure n (%)	53 (69.7)	37 (80.4)	43 (70.5)
		95% CI	58.1, 79.8	66.1, 90.6	57.4, 81.5
		Clinical Failure/Indeterminate n (%)	23 (30.3)	9 (19.6)	18 (29.5)
		Clinical Failure n (%)	18 (23.7)	6 (13.0)	17 (27.9)
		Indeterminate n (%)	5 (6.6)	3 (6.5)	1 (1.6)
	Follow-Up	Clinical Cure n (%)	42 (55.3)	32 (69.6)	38 (62.3)
		95% CI	43.4, 66.7	54.2, 82.3	49.0, 74.4
		Clinical Failure/Indeterminate n (%)	34 (44.7)	14 (30.4)	23 (37.7)
		Clinical Failure n (%)	25 (32.9)	10 (21.7)	21 (34.4)
		Indeterminate n (%)	9 (11.8)	4 (8.7)	2 (3.3)

Notes	Clinical cure rates were 80.4% in Group 2, 69.7% in Group 1, and 70.5% in caspofungin. The most common reasons for failure in all groups were lack of resolution of attributable signs and symptoms or requirement for new/prolonged therapy. Clinical cure rates were slightly higher in the investigator-assessed response compared with the overall response, although with a similar pattern with the highest response rate in Group 2. Incidence of indeterminate response at Day 14 was lower in the investigator's assessment of clinical response compared with the overall response. Clinical cure rates in the mITT2 Population were 70.0%, 86.7%, and 60.0%, and in the mITT3 Population were 66.0%, 88.9%, and 63.0% in Group 1, Group 2, and caspofungin, respectively. Compared with the clinical cure rates in the mITT Population, rates in the mITT2 Population were similar for Group 1, higher for Group 2, and lower for caspofungin. Compared with the clinical cure rates in the mITT Population, rates in the mITT3 Population were lower for Group 1, higher for Group 2, and lower in caspofungin.

Table 2 Summary of efficacy for trial ReSTORE

Title: A Phase 3, Multicenter, Randomized, 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 Invasive Candidiasis			
Study identifier	Protocol number: CD101.IV.3.05 EudraCT number: 2018-002630-21 ClinicalTrials.gov Identifier: NCT03667690		
Design	multicenter, prospective, randomized, double-blind, efficacy and safety study of rezafungin for injection (IV) versus a comparator regimen of caspofungin (IV) followed by optional oral fluconazole stepdown therapy in subjects with candidemia and/or invasive candidiasis.		
	Duration of main phase:		63 days
Hypothesis	Non-inferiority		
Treatments groups	Rezafungin		Treatment: rezafungin Duration: 2-4 weeks Number randomized: 100
	Caspofungin with oral stepdown option		Treatment: caspofungin Duration: 2-4 weeks Number randomized: 99
Endpoints and definitions	Primary endpoint	Global cure Day 14	Global cure (based on clinical cure as assessed by the Investigator, radiological cure [for qualifying IC subjects], and mycological eradication) at Day 14 (±1 day)
	Secondary endpoint 1	ACM Day 30	All-Cause Mortality at Day 30
	Secondary endpoint 2	Global cure by visit	Global cure at Day 5, Day 30 (-2 days), EOT (≤2 days of last dose), and Follow-up (Days 52–59) visit
	Secondary endpoint 3	Mycological eradication by visit	Mycological eradication at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (⩽2 days of last dose), and Follow-up (Days 52 – 59) visit
	Secondary endpoint 4	Clinical cure by visit	Clinical cure as assessed by the Investigator at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (⩽2 days of last dose), and Follow-up (Days 52 – 59) visit

Title: A Phase 3, Multicenter, Randomized, 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 Invasive Candidiasis			
Study identifier	Protocol number: CD101.IV.3.05 EudraCT number: 2018-002630-21 ClinicalTrials.gov Identifier: NCT03667690		
	Secondary endpoint 5	Radiological cure by visit	Radiological cure for IC subjects at Day 5, Day 14 (±1 day), Day 30 (-2 days), EOT (⩽2 days of last dose), and Follow-up (Days 52 – 59)
Database lock	30 November 2021		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified intent to treat (n=187) defined as subjects who had a documented *Candida* infection based on Central Laboratory evaluation of a culture from blood or another normally sterile site obtained ⩽4 days (96 hours) before randomization and received ⩾1 dose of study drug time point: postrandomisation through follow-up visit		
Descriptive statistics and estimate variability	Treatment group	Rezafungin	Caspofungin with oral stepdown option
	Number of subjects	93	94
	Global cure Day 14 (number, percentage)	55 (59.1%)	57 (60.6%)
Effect estimate per comparison	Global cure Day 14	Comparison groups	Rezafugin to Caspofungin with oral stepdown option
		difference between groups	-1.1
		95% Confidence interval	-14.9, 12.7

Analysis description	**Secondary analysis**		
Analysis population	Modified intent to treat		
Descriptive statistics and estimate variability	Treatment group	Rezafungin	Caspofungin with oral stepdown option
	Number of subjects	93	94
	ACM Day 30 (number, percentage)	22 (23.7%)	20 (21.3%)
	Global cure by visit (number, percentage)	Day 5: 52 (55.1%) Day 30: 46 (49.5%) EOT: 56 (60.2%) FU: 42 (45.2%)	Day 5: 49 (52.1%) Day 30: 46 (48.9%) EOT: 59 (62.8%) FU: 39 (41.5%)
	Mycological eradication by visit (number, percentage)	Day 5: 64 (68.8%) Day 14: 63 (67.7%) Day 30: 56 (60.2%) EOT: 63 (67.7%) FU: 48 (51.6%)	Day 5: 58 (61.7%) Day 14: 63 (66.0%) Day 30: 53 (56.4%) EOT: 63 (67.0%) FU: 49 (52.1%)
	Clinical cure by visit (number, percentage)	Day 5: 59 (63.4%) Day 14: 62 (66.7%) Day 30: 51 (54.8%) EOT: 65 (69.9%) FU: 46 (49.5%)	Day 5: 70 (74.5%) Day 14: 63 (67.0%) Day 30: 52 (55.3%) EOT: 64 (68.1%) FU: 44 (46.8%)

	Radiological cure by visit (number, percentage)	Day 5: 4 (26.7%), n=15 Day 14: 11 (64.7%), n=17 Day 30: 10 (58.8%), n=17 EOT: 9 (56.3%), n=16 FU: 46 (49.5%), n=17	Day 5: 6 (35.3%), n=17 Day 14: 10 (58.8%), n=17 Day 30: 11 (64.7%), n=17 EOT: 11 (64.7%), n=17 FU: 10 (58.8%), n=17
Effect estimate per comparison	ACM Day 30	Comparison groups	Rezafugin to Caspofungin with oral stepdown option
		difference between groups	2.4
		95% Confidence interval	-9.7, 14.4
	Global cure by visit	Comparison groups	Rezafugin to Caspofungin with oral stepdown option
		difference between groups	Day 5: 3.8 Day 30: 0.5 EOT: -2.6 FU: 3.7
		95% Confidence interval	Day 5: -10.5, 17.9 Day 30: -13.7, 14.7 EOT: -16.4, 11.4 FU: -10.5, 17.7
	Mycological eradication by visit	Comparison groups	Rezafugin to Caspofungin with oral stepdown option
		difference between groups	Day 5: 7.1 Day 14: 1.8 Day 30: 3.8 EOT: 0.7 FU: -0.5
		95% Confidence interval	Day 5: -6.6, 20.6 Day 14: -11.7, 15.2 Day 30: -10.3, 17.8 EOT: -12.7, 14.1 FU: -14.7, 13.7
	Clinical cure by visit	Comparison groups	Rezafugin to Caspofungin with oral stepdown option
		difference between groups	Day 5: -11 Day 14: -0.4 Day 30: -0.5 EOT: 1.8 FU: 2.7
		95% Confidence interval	Day 5: -24.0, 2.3 Day 14: -13.8, 13.1 Day 30: -14.6, 13.7 EOT: -11.5, 15.0 FU: -11.6, 16.8
	Radiological cure by visit	Comparison groups	Rezafugin to Caspofungin with oral stepdown option

		difference between groups	Day 5: -8.6 Day 14: 5.9 Day 30: -5.9 EOT: -8.5 FU: 11.8
		95% Confidence interval	Day 5: -39.0, 24.1 Day 14: -26.3, 37.0 Day 30: -37.0, 26.3 EOT: -39.9, 24.5 FU: -20.5, 41.8

2.6.5.1. Clinical studies in special populations

Only adult subjects were included in the reported studies. Subjects older than 65 years old were included in these studies (+/- 40% in each treatment arm in both studies). The integrated subgroup analysis of ACM at Day 30 showed a lower mortality rate in those aged >65 years (ACM at Day 30 [-2 days] of 14.0%, 8/57 versus 31.7%, 20/63 in caspofungin arm; weighted treatment difference of -17.6 [95% CI: -32.5 to -2.8]

Table 24. Age of Subjects Receiving Rezafungin in Clinical Studies (Safety Population)

Type of Trial	Phase	Age (Years), n (%)			
		18-64	65-74	75-84	85+
Controlled Trials	All Studies (N = 409)	310 (75.8)	60 (14.7)	29 (7.1)	10 (2.4)
	Phase 1 (N = 177)	174 (98.3)	3 (1.7)	0 (0.0)	0 (0.0)
	Phase 2 (STRIVE) (N = 134*)	78 (58.2)	35 (26.1)	17 (12.7)	4 (3.0)
	Phase 3 (ReSTORE) (N = 98)	58 (59.2)	22 (22.4)	12 (12.2)	6 (6.1)
Non-Controlled Trials	All Studies (N = 0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Compassionate Use	N/A (N = 17†)	11 (64.7)	4 (23.5)	1 (5.9)	0 (0.0)

N: number of subjects; n: Number of subjects in the category; N/A: not applicable
* Phase 2 data includes subjects treated with rezafungin in both Group 1 (400/400 mg) and Group 2 (400/200 mg)
† Compassionate use data correct up to 28 February 2023. Compassionate use data includes one patient <18 years old (15 years old)

2.6.5.2. Analysis performed across trials (pooled analyses and meta-analysis)

Efficacy

The design of the Phase 2 STRIVE and Phase 3 ReSTORE studies were nearly identical although definitions of some efficacy outcome measures differed. Therefore, prior to unblinding of the Phase 3 data, combined analyses were planned. Rezafungin 400/200 mg and caspofungin groups in the Phase 2 STRIVE and Phase 3 ReSTORE studies were integrated for analyses of the following efficacy endpoints (in the mITT Analysis Set as defined in the Phase 3 ReSTORE study):

a. All-cause mortality (ACM), 30-day ACM was the primary efficacy outcome in Phase 3 ReSTORE): ACM is an objective endpoint which is appropriate for an integrated analysis and was also assessed as a safety endpoint (ACM through the Follow-up visit in the Safety Analysis Set). Subgroup analyses of ACM were conducted.

b. Mycological response: Analyses of by-subject mycological response, mycological response by *Candida* spp., mycological response by *Candida* spp. and MIC value, and mycological response by *Candida* spp. and disk zone diameter were conducted at Day 5 and Day 14. Mycological response was defined slightly differently in the Phase 2 STRIVE and Phase 3 ReSTORE studies; however, data are available in the case report forms (CRFs) to standardise the definition to that used in the Phase 3 ReSTORE study. Integrated analyses of mycological response provided a more robust determination of efficacy by *Candida* spp. given the larger sample size.

Integrated analyses of global response (primary outcome in the Phase 3 ReSTORE study for the EMA) was not conducted, as the Phase 2 STRIVE and Phase 3 ReSTORE outcomes differed in important ways. In the Phase 3 ReSTORE study, global response was determined from clinical response, radiological response, and mycological eradication as determined by an independent DRC. The Phase 2 STRIVE study did not include a DRC and radiological response was not collected on the CRF.

a. All-cause mortality (ACM), 30-day ACM was the primary efficacy outcome in Phase 3 ReSTORE):

Among the pooled groups, the rate of subjects who were either known to be deceased or with unknown survival status was 18.7% and 19.4% in the rezafungin and caspofungin groups, respectively. Non-inferiority of rezafungin was demonstrated (weighted treatment difference of -1.5 [95% CI: -10.7 to 7.7]), with the upper limit of the 95% CI for the difference in the mITT Population lower than 20%. Superiority of rezafungin was not demonstrated given the upper bound of the 95% CI of 7.7.

Characteristic, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin (Group 1: 400/400 mg) (N = 76)	Rezafungin (Group 2: 400/200 mg) (N = 46)	Caspofungin (70/50 mg) (N = 61)	Rezafungin (400/200 mg) (N = 93)	Caspofungin (70/50 mg) (N = 94)	Rezafungin (400/200 mg) (N = 139)	Caspofungin (70/50 mg) (N = 155)
Deceased [a]	18 (23.7)	4 (8.7)	10 (16.4)	22 (23.7)	20 (21.3)	26 (18.7)	30 (19.4)
Known deceased	12 (15.8)	2 (4.3)	8 (13.1)	19 (20.4)	17 (18.1)	21 (15.1)	25 (16.1)
Unknown survival status	6 (7.9)	2 (4.3)	2 (3.3)	3 (3.2)	3 (3.2)	5 (3.6)	5 (3.2)
Alive	58 (76.3)	42 (91.3)	51 (83.6)	71 (76.3)	74 (78.7)	113 (81.3)	125 (80.6)
Difference in death rate (95% CI) [b,c,d]	--	-7.0 (-21.2, 7.3)		2.4 (-9.7, 14.4)		-1.5 (-10.7, 7.7)	

The ACM endpoint was the preferred by FDA. In Phase 3, the lower bound of the CI was within -10%. This finding is supported by ACM rates observed in Phase 2, albeit in much smaller numbers. The ACM findings are supportive of the efficacy of the selected rezafungin dose.

b. Mycological response:

Mycological Response at Day 5 and Day 14, Integrated Data

Among the pooled groups, the rate of subjects with mycological eradication at Day 5 was 73.4% and 64.5% in the rezafungin and caspofungin groups, respectively (weighted treatment difference of 10.0 [95% CI: -0.3 to 20.4]). At Day 5, the indeterminate rate in the rezafungin group (3.6%) was approximately half that of the caspofungin group (6.5%). In the individual studies, the rate of subjects with mycological eradication at Day 5 for the Phase 2 STRIVE study was 82.6% in rezafungin Group 2 and 68.9% in the caspofungin group (weighted [by Part A and Part B] treatment difference of 14.3 [95% CI: -1.8 to 30.4]) and the rate of subjects with mycological eradication at Day 5 for the Phase 3 ReSTORE study was 68.8% in the rezafungin group and 61.7% in the caspofungin group (treatment difference of 7.1 [95% CI: 6.6 to 20.6]).

Mycological eradication rates were comparable across treatment groups at Day 14. Among the pooled groups, the rate of subjects with mycological eradication at Day 14 was 71.9% and 68.4% in the rezafungin and

caspofungin groups, respectively (weighted treatment difference of 4.3 [95% CI: -6.2 to 14.7]). At Day 14, the indeterminate rates in the pooled treatment groups were similar. In the individual studies, the rate of subjects with mycological eradication at Day 14 for the Phase 2 STRIVE study was 80.4% in rezafungin Group 2 and 72.1% in the caspofungin group (weighted [by Part A and Part B] treatment difference of 8.0 [95% CI: -8.5 to 24.6]) and the rate of subjects with mycological eradication at Day 14 for the Phase 3 ReSTORE study was 67.7% in the rezafungin group and 66.0% in the caspofungin group (treatment difference of 1.8 [95% CI: -11.7 to 15.2]).

Visit Response, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin (Group 1: 400/400 mg) (N = 76)	Rezafungin (Group 2: 400/200 mg) (N = 46)	Caspofungin (70/50 mg) (N = 61)	Rezafungin (400/200 mg) (N = 93)	Caspofungin (70/50 mg) (N = 94)	Rezafungin (400/200 mg) (N = 139)	Caspofungin (70/50 mg) (N = 155)
Day 5							
Eradication	54 (71.1)	38 (82.6)	42 (68.9)	64 (68.8)	58 (61.7)	102 (73.4)	100 (64.5)
Failure or Indeterminate	22 (28.9)	8 (17.4)	19 (31.1)	29 (31.2)	36 (38.3)	37 (26.6)	55 (35.5)
Failure	15 (19.7)	7 (15.2)	18 (29.5)	25 (26.9)	27 (28.7)	32 (23.0)	45 (29.0)
Indeterminate	7 (9.2)	1 (2.2)	1 (1.6)	4 (4.3)	9 (9.6)	5 (3.6)	10 (6.5)
Difference in eradication rate (95% CI) [a,b,c]	--	14.3 (-1.8, 30.4)		7.1 (-6.6, 20.6)		10.0 (-0.3, 20.4)	
Day 14							
Eradication	54 (71.1)	37 (80.4)	44 (72.1)	63 (67.7)	62 (66.0)	100 (71.9)	106 (68.4)
Failure or Indeterminate	22 (28.9)	9 (19.6)	17 (27.9)	30 (32.3)	32 (34.0)	39 (28.1)	49 (31.6)
Failure	17 (22.4)	8 (17.4)	17 (27.9)	26 (28.0)	28 (29.8)	34 (24.5)	45 (29.0)
Indeterminate	5 (6.6)	1 (2.2)	0 (0.0)	4 (4.3)	4 (4.3)	5 (3.6)	4 (2.6)
Difference in eradication rate (95% CI) [a,b,c]	--	8.0 (-8.5, 24.6)		1.8 (-11.7, 15.2)		4.3 (-6.2, 14.7)	

Additional integrated analyses of subgroups were performed suggesting advantages of rezafungin over caspofungin (these data should be considered preliminary):

In the subgroup of mITT subjects who had a positive culture proximal to randomisation, the rate of subjects with mycological eradication at Day 5 was 75.5% and 54.9% in the rezafungin and caspofungin groups, respectively (weighted treatment difference of 19.2 [95% CI: 3.0 to 35.5]). These results carried on through day 14 with subjects who had a positive culture proximal to randomisation, having a mycological eradication rate of 75.5% and 62.0% in the rezafungin and caspofungin groups, respectively (weighted treatment difference of 13.4 [95% CI: -2.8 to 29.5]). In subjects with a final diagnosis for candidaemia only, those with positive *Candida* culture proximal to randomisation in the mITT Population the rate of subjects with mycological eradication at Day 14 was 74.4% and 64.6% in the rezafungin and caspofungin groups, respectively (weighted treatment difference of 7.6 [95% CI: -11.5 to 26.7]). In subjects with a final diagnosis of IC, the rate of subjects with mycological eradication at Day 14 was 69.2% and 62.5% in the rezafungin and caspofungin groups, respectively (weighted treatment difference of 10.4 [95% CI: -9.1 to 29.8]).

For pooled analyses across the Phase 2 and Phase 3 studies, the median total number days in ICU was 10.0 days in the rezafungin group compared to 16 days in the caspofungin group.

The subgroup of patients who had an Apache II score of ≥20 had an ACM at Day 30 of 5/21 (23.8%) in the rezafungin group and 10/26 (38.5%) in caspofungin group. This coincided with improved mycological eradication at Day 5 in Apache II of ≥20 (14/21; 81.0%) with rezafungin when compared to caspofungin (16/26; 61.5%). A similar pattern was seen at Day 14 (14/26; 66.7% versus 34/59; 57.6%, respectively).

Integrated analyses showed a lower mortality rate in those aged >65 years (ACM at Day 30 [-2 days] of 14.0%, 8/57 versus 31.7%, 20/63 in caspofungin arm; weighted treatment difference of -17.6 [95% CI: -32.5 to -2.8]).

Mortality rates for *C. parapsilosis* (1/14 [7.1%] for rezafungin versu 8/27 [29.6%] for caspofungin) and *C. tropicalis* (5/27 [18.5%] versus 7/22 [31.8%], respectively) showed the largest difference between the treatment groups.

Mycological response rates for *C. parapsilosis* (11/14 [78.6%] for rezafungin versus 18/27 [66.7%] for caspofungin), *C. glabrata* (29/38 [76.3%] versus 21/35 [60%], respectively) and *C. tropicalis* (22/27 [81.5%] versus 12/22 [54.5%], respectively) showed the largest difference between the treatment groups at Day 5.

Microbiology

The *Summary of Clinical Pharmacology* provides an overall view of the *in vitro* susceptibility of clinical isolates from sponsored studies to rezafungin. The following tables provide the MIC range and $MIC_{50/90}$ of rezafungin for baseline *Candida* spp by treatment group and by region for the mITT population.

Table 43. Summary of rezafungin activity against baseline *Candida* spp. overall and by treatment group (mITT; pooled data)

Organism	Summary of Rezafungin Activity (mg/L; Pooled)								
	Rezafungin 400/200 mg (N=139)			Caspofungin 70/50 mg (N=155)			Overall (N=294)		
	n	Range	$MIC_{50/90}$	n	Range	$MIC_{50/90}$	n	Range	$MIC_{50/90}$
C. albicans	59	0.0005-0.004	0.001/0.004	69	0.0005-0.015	0.001/0.002	128	0.0005-0.015	0.001/0.004
C. glabrata	38	0.004-0.5	0.008/0.015	35	0.004-0.03	0.008/0.008	73	0.004-0.5	0.008/0.008
C. tropicalis	27	0.002-0.015	0.008/0.008	22	0.002-0.008	0.008/0.008	49	0.002-0.015	0.008/0.008
C. parapsilosis	14	0.25-2	1/2	27	0.25-2	1/2	41	0.25-2	1/2
C. krusei	5	0.008-0.015	-	3	0.008-0.015	-	8	0.008-0.015	-
C. dubliniensis	2	0.004	-	2	0.004	-	4	0.004	-
C. guilliermondii	2	0.12-0.5	-	-	-	-	2	0.12-0.5	-
C. lusitaniae	1	0.008	-	1	0.008	-	2	0.008	-
C. metapsilosis	3	0.06-0.12	-	-	-	-	5	0.06-0.12	-
C. nivariensis	-	-	-	1	0.004	-	1	0.004	-
C. kefyr	-	-	-	1	0.004	-	1	0.004	-
C. intermedia	-	-	-	1	0.002	-	1	0.002	-

n, number of subjects with the specified species at baseline; N, number of subjects.
Source: Data on file

Table 44. Summary of rezafungin activity against baseline *Candida* spp. by region (mITT; pooled data)

Organism	Summary of Rezafungin Activity (mg/L; Pooled)								
	N. America/S. America (N=89)			Europe/Israel/Turkey (N=143)			Asia/Pacific (N=62)		
	n	Range	$MIC_{50/90}$	n	Range	$MIC_{50/90}$	n	Range	$MIC_{50/90}$
C. albicans	44	0.0005-0.0015	0.001/0.004	63	0.0005-0.004	0.002/0.002	18	0.0005-0.004	0.002/0.004
C. glabrata	28	0.004-0.015	0.008/0.008	31	0.004-0.5	0.008/0.008	11	0.08-0.015	0.008/0.015
C. tropicalis	9	0.002-0.008	-	15	0.004-0.015	0.008/0.008	18	0.004-0.008	0.008/0.008
C. parapsilosis	5	0.5-2	-	31	0.25-2	1/2	4	0.25-1	-
C. krusei	2	0.015	-	5	0.008-0.015	-	1	0.015	-
C. dubliniensis	2	0.004	-	1	0.004	-	1	0.004	-
C. guilliermondii	-	-	-	1	0.5	-	1	0.12	-
C. lusitaniae	2	0.008	-	-	-	-	-	-	-
C. metapsilosis	2	0.06-0.12	-	1	0.12	-	-	-	-
C. nivariensis	-	-	-	1	0.004	-	-	-	-
C. kefyr	-	-	-	1	0.004	-	-	-	-
C. intermedia	1	0.002	-						

n, number of subjects with the specified species at baseline; N, number of subjects.
Source: Data on file

There was little to no apparent difference in rezafungin activity based on treatment group or region. MIC ranges and $MIC_{50/90}$ values were identical or within 2-fold for isolates recovered from rezafungin-treated and caspofungin treated subjects at baseline and across regions.

Based on $MIC_{50/90}$ and range, there was no apparent regional variation in rezafungin activity. For the five most commonly encountered species (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis* and *C. krusei*), rezafungin MIC distributions for clinical trial isolates were consistent with those observed during EDL multi-centre study using the modified EUCAST susceptibility testing methodology.

There were only two subjects in ReSTORE with isolates that tested non-susceptible to an echinocandin at baseline. One subject, who had a *C. glabrata* carrying a mutation in Fks2 at baseline, had a successful mycological response at Day 14 (but was a mycological failure at Day 5) and was alive at Day 30. The other Subject, who had a *C. glabrata* baseline isolate with a rezafungin MIC of 0.008 mg/L but no *FKS* mutations, had a successful mycological outcome at Days 5 and 14 and was alive at Day 30.

In the ReSTORE study, 11 isolates were resistant to fluconazole at baseline, of which 4 were treated with rezafungin (400/200 mg). Due to the limited number of subjects with fluconazole-resistant isolates, it is difficult to draw any definitive conclusion regarding any potential impact of fluconazole-resistance on the outcome of subjects treated with either rezafungin or caspofungin, although fluconazole-resistance had no apparent impact on the MIC of echinocandins.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Two controlled clinical studies have been carried out to investigate the efficacy of rezafungin in the treatment of IC. Both studies enrolled subjects presenting with systemic signs of candidemia and/or IC and with an established mycological diagnosis of candidemia and/or IC from a sample taken ≤ 96 hours before randomisation defined as ≥1 blood culture positive for yeast or *Candida*, OR positive test for *Candida* from a sponsor-approved rapid in vitro diagnostic (IVD), OR positive Gram stain for yeast or positive culture for Candida spp. from a specimen obtained from a normally sterile site.

Rezafungin dose regimen selected for Phase 3

The dose-finding study compared two rezafungin weekly regimens with caspofungin for treatment of IC in a population similar to that which was later enrolled into Phase 3 studies.

Both the dosing regiments from the Phase 2 study were considered for progression into the Phase 3 study. The dose selection for the Phase 3 study was supported by preclinical PK/PD studies and an updated population PK model that contained patient data. Given the target attainment analysis and the results of the Phase 2 study which demonstrated that a dosing regimen of 400/200 mg had a good safety and tolerability profile and was at least as efficacious as caspofungin, it was proposed that this dose (400/200 mg) would be taken into the Phase 3 study as the benefit-risk was considered highest for this dosing regimen.

Primary endpoint

For the Phase 2 study, the primary efficacy outcome was Overall Response at Day 14 defined as mycological eradication AND resolution of attributable systemic signs of candidemia and/or IC that were present at baseline, no change of antifungal therapy for the treatment of candidemia and/or IC, and the subject was not lost to follow-up on the day of assessment.

The primary efficacy outcome for the Phase 3 ReSTORE study was global cure (based on clinical cure as assessed by the Investigator, radiological cure [for qualifying IC subjects], and mycological eradication) confirmed by a blinded independent DRC at Day 14 (±1 day).

Analysis populations

The primary analysis was conducted in the modified intent-to-treat population (subjects who receive any amount of study drug and with documented *Candida* infection confirmed from a blood culture obtained within 96 hours of randomization or from a specimen obtained from a normally sterile site).

Given that patients were allowed to receive empirical antifungal therapy prior to randomisation and that biologic samples obtained 4 days before randomisation could be impacted from previous antifungal therapy, additional populations were analysed which required a reduction in time from collection of biologic samples for confirmation of Candida infection to randomisation (mITT2 and mITT3) in response to concerns raised by the EMA during scientific advice (EMA/CHMP/SAWP/596942/2018).

Sample size calculations

For both studies sample size calculations were well justified. Only for Restore there were inferential analysis resorting to two-sided 95% CI (adjusted for the randomisation stratification factors) for the observed between-group difference in global cure rate in the mITT Population using the method of Miettinen and Nurminen. This is a robust method for constructing confidence intervals of the difference in binomial proportions.

Efficacy data and additional analyses

The efficacy of rezafungin in the treatment of candidaemia and invasive candidiasis was considered comparable to caspofungin plus step-down therapy, with regards to global response at Day 14 and ACM at Day 30. However, the justification for the chosen NIM of -20% is primarily based on ACM as this provides an indication of failure for Global Response, whereas the actual Global Response benefit would be larger than ACM when including the benefit derived regarding non-fatal failures. This margin was discussed with the CHMP /SAWP, it was noted that "meeting a 20% NIM in a single pivotal trial with an observed lower bound of the 95% CI that is >-20% but <-10% could result in an indication that is restricted to patients with limited treatment options". Although it is acknowledged that a 10% NIM would have required quadruple the number of patients compared with a 20% NI margin the fact that the point estimate was -1.1 thus lower rate of global cure for the rezafungin group compared to the caspofungin group could in fact limit the interpretation the indication of the product. The applicant themselves stated that, although the lower level of the 95% CI resulted in a NI outcome of -14.9%, the true benefit of rezafungin to patients is supported by the clear and consistently positive outcomes across a wide range of endpoints, the data are still limited to support that this echinocandin should be considered as effective as others in the same class. Even if the CI was -14.9, thus very close to -15, the sample size was calculated for a NIM of 20% thus the effect might or might not hold with a different sample size.

Although analysis of pooled data suggests the same results of non-inferiority, these are reported for ACM and Mycological Response not for the primary outcome assessed in the Restore study.

Further to this, the small numbers of neutropenic patients (7,5% of patients in the Phase 3 study) preclude reliable conclusions for comparisons between treatment groups. Hence, the efficacy of rezafungin in this population is not established. Similarly, only 16.6% of patients had APACHE II scores ≥ 20. This cannot be considered sufficient to reach definitive conclusion on efficacy and optimal dose of rezafungin in such seriously ill patients.

Secondary and exploratory analyses are consistent with the primary analysis and some of them suggest potential benefits of rezafungin over caspofungin. One of them is the reduced (but not significantly different) median time to obtain a negative blood culture with rezafungin, although this was not translated in the results obtained in the primary analysis.

In the pooled analyses, there appeared to be a positive correlation between improved mycological response and proximity of blood culture to randomisation in the rezafungin versus caspofungin groups. Similar trends were also noted in analyses of mortality and mycological response; responses in the elderly and frail; in mortality and mycological response by ICU stay; and in efficacy against certain non-*albicans Candida* species. Nevertheless, these analyses were not powered to show statistical significance and should be seen at this stage, to be preliminary.

2.6.7. Conclusions on the clinical efficacy

From the results of the pivotal Phase 3 study, rezafungin was considered non-inferior to caspofungin plus oral step-down therapy in the treatment of patients with candidemia or other forms of IC. However, the chosen non-inferiority margin in this comparative study can be considered as being too wide (20%). Even if the applicant states that although the lower level of the 95% CI resulted in a NI outcome of -14.9%, and that the true benefit of rezafungin to patients is supported by the clear and consistently positive outcomes across a wide range of endpoints, the data is still limited to support that this echinocandin should be considered as effective as others in the same class. Even if the CI was -14.9, thus very close to -15, the sample size was calculated for a NIM of 20% thus the effect might or might not hold with a different sample size.

Even with a NIM of 15%, the outcome with a lower bound of the 95% CI of the difference in Global response compared with caspofungin (slightly above -15%) and the upper bound of the 95% CI of the difference in ACM (slightly below 15%), which was the FDA primary endpoint, raises concerns of a potential unacceptable loss of antifungal effect, which might not be compatible with clinical utility. The applicant was asked to further justify that the clinical efficacy data supports a positive benefit-risk balance for the intended indication.

The applicant did not provide any significantly different information in comparison to the originally submitted data. Given the difficulty in the recruitment of patients, it is understood that the non-inferiority margin of 20% was chosen to allow for a reasonable number of subjects included in a smaller period of time.

The concerns raised by the pre-defined primary analysis results are not wholly resolved by the applicant's multiple alternative analyses presented, including several *post hoc* analyses. Effectively, the indication comes down to an overall opinion on the following results:

	REZZAYO 400 mg/200 mg N = 93 n (%)	Caspofungin 70 mg/50 mg N = 94 n (%)	Difference (95% CI) [a]
All-Cause Mortality (Day 30) [b]	22 (23.7)	20 (21.3)	2.4 (-9.7, 14.4)
Global Cure [c]			
Day 5	52 (55.9)	49 (52.1)	3.8 (-10.5, 17.9)
Day 14	55 (59.1)	57 (60.6)	-1.5 (-15.4, 12.5)
Clinical Cure [d]			
Day 5	59 (63.4)	70 (74.5)	-11.0 (-24.0, 2.3)
Day 14	62 (66.7)	63 (67.0)	-0.4 (-13.8, 13.1)
Day 30	51 (54.8)	52 (55.3)	-0.5 (-14.6, 13.7)
Mycological eradication/presumed eradication [e]			
Day 5	64 (68.8)	58 (61.7)	7.1 (-6.6, 20.6)
Day 14	63 (67.7)	62 (66.0)	1.8 (-11.7, 15.2)

[a] Two-sided 95% confidence intervals (CIs) for the observed differences in cure rates (REZZAYO minus caspofungin) is calculated using the unadjusted methodology of Miettinen and Nurminen.
[b] Patients who died on or before Day 30, or with unknown survival status.
[c] Patients with a mycological eradication/presumed eradication, clinical cure and radiologic cure (for patients with IC documented by radiologic or other imaging findings at baseline), as adjudicated by the Data Review Committee.
[d] Investigator's assessment of clinical response based on resolution of attributable systemic signs and symptoms of candidemia/IC, no new systemic signs or symptoms attributable to candidemia/IC, no new systemic antifungal therapy to treat candidemia/IC, and the subject is alive.
[e] Negative blood culture or culture from a normally sterile site and no change in antifungal therapy for the treatment of candidemia and/or IC. For IC patients, if the normally sterile baseline site of *Candida* infection was not accessible, the patient was presumed to have an eradication if the clinical outcome and radiologic outcome (if assessed) was a cure.

This study was designed and powered to address both the FDA-preferred (ACM) and the EU-preferred (global response) primary endpoints.

For the EU-recommended primary endpoint, the previously reported Day 14 analysis of global cure gives a lower bound of the CI that is just below 15%. The lower bound of the 95% CI was within -10% for the FDA-recommended primary endpoint of ACM at day 30 in the mITT population.

For clinical cure, the analyses at each timepoint suggest that rezafungin is not as effective as caspofungin. However, the day 5 results for global cure and the day 5 and 14 results for mycological eradication are generally supportive of comparable efficacy.

It is also recognized that the secondary and exploratory endpoints from the ReSTORE study, as well as sensitivity analysis, support the results obtained for the primary endpoint. However, the greater than 10% NIM chosen provides some uncertainty in the compared efficacy of rezafungin with caspofungin (or other echinocandins).

The applicant had not been able to establish that rezafungin has any clear advantages in terms of spectrum, efficacy or safety over the approved agents in the same class for treatment of candidiasis. At the same time, there are relatively few antifungal agents available and the overall assessment of the efficacy findings, including the results for the pre-defined primary endpoint of ACM at day 30 (although not the EU-preferred primary endpoint), supports a conclusion that rezafungin has efficacy in the population studied.

The applicant was therefore asked to provide additional data regarding clinical efficacy and safety of rezafungin in neutropenic patients (e.g. observational studies, compassionate use) to support the approval of an indication that includes this population.

The Applicant recognised that the number of neutropenic subjects included in the dataset is small, but it is as expected and is in line with other IC studies in neutropenic subjects. These subjects often have prophylactic antifungal treatment and are difficult to recruit into clinical studies of IC. However, there is nothing to suggest that rezafungin performs differently, in terms of benefits and risks, in neutropenic vs non-neutropenic subjects, or when compared with caspofungin in neutropenic subjects. Regarding Safety, no serious treatment-related adverse events were observed with rezafungin in neutropenic subjects in the development programme. However, to reflect the small numbers of subjects with an ANC <500, the following text was included in the SmPC:

Section 4.4: "*Efficacy of rezafungin was only evaluated in a small number of neutropenic subjects (see Section 5.1)*".

Section 5.1: "*For rezafungin and caspofungin treatment groups, 88.0% and 93.9% subjects, respectively, had an ANC ≥ 500/mm^3 at baseline.*"

Neutropenic subjects have a compromised immune system and are therefore at particular risk from infections. These subjects are particularly in need of effective anti-infective treatments. Echinocandins have been shown to have a positive benefit-risk assessment in neutropenic subjects and rezafungin treatment data do not suggest it should perform differently in these subjects. The non-restricted indications for the already approved echinocandins was supported by more data in patients with neutropenia than in the case of Rezzayo. The data for other echinocandins showed that efficacy can be anticipated in neutropenic patients at the same dose level as in non-neutropenic patients. Therefore, although the data in neutropenic patients are limited in this case, similar effects in non-neutropenic and neutropenic patients at the same dose level could be anticipated also for Rezzayo.

Considering that there was a limited number of neutropenic subjects included for analysis but also that the submitted data does not suggest a diminished efficacy of rezafungin in patients with neutropenia (as with other echinocandins), the inclusion of this population in the proposed indication is acceptable. The information regarding this issue included in sections 4.4 and 5.1 of the SmPC was acceptable to the CHMP.

2.6.8. Clinical safety

Safety data from the eight completed Phase 1 studies was provided for the individual studies.

The most relevant safety data comes from the Phase 2 study STRIVE group 2 and Phase 3 study ReSTORE, as the design are nearly identical and the rezafungin dosing used was the 400/200 mg one (the same that is intended for approval). Safety data discussed for these studies is presented in the form of pooled data. For the most part, this section describes the safety data by Phase 2 STRIVE group 2 and Phase 3 study as reported in each CSR. Some additional tables are provided from the applicant's *Summary of safety* in which the pooling of studies was made and some data from Phase 1, depending on the safety point being reviewed.

Rezafungin is also in development for the prevention of (invasive fungal disease [IFD]) in the allogeneic bone marrow transplant population; no data from this study, namely regarding safety, is included as part of this marketing authorization application, and no data regarding those ongoing studies was provided.

Eight patients were included in the expanded access program, that provided access to rezafungin for subjects with IFD and limited treatment options and who do not otherwise qualified to be included in an ongoing clinical study. No new safety signals have been identified in these patients.

2.6.8.1. Patient exposure

A summary of the study drug administration by study is shown in Table 4.

A total of 409 subjects have been exposed to at least 1 dose of rezafungin for a duration between 1 and 28 Days as shown in Table 5.

Table 4. Summary of Study Drug Administration

Study Number	Study Title	Number of Subjects/ Dose, Subjects/ Regimen
Safety and Pharmacokinetics		
CD101.IV.1.01	A Phase 1, Randomised, 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, 6 100 mg, once weekly; 2 doses 200 mg, once weekly; 2 doses 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: 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) 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 Co-administered 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 versus Intravenous Caspofungin Followed by Oral Fluconazole Step-down in the Treatment of Subjects with Candidemia and/or IC (STRIVE study)	Parts A and B: 202 subjects/ Group 1: rezafungin: 400 mg weekly × 2 to 4 weeks total, rezafungin: 81 dosed; Group 2: rezafungin: 400 mg on Day 1, followed by 200 mg once weekly × 2 to 4 weeks total, 53 dosed; 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); Caspofungin: 98 dosed daily
IC: Invasive candidiasis.		

Table 5. 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 in patient-months	**184.2 patient-months**
IV: Intravenous.	

Study drug duration of exposure is summarised in Table 6 for the Safety Population from the Phase 2 STRIVE and Phase 3 ReSTORE studies. The duration of treatment ranged from 1 to 28 days, and median duration of treatment (IV and oral therapy combined) was identical in all study treatment groups and pooled data at 14.0 days.

Both IV and oral therapy had similar median duration of treatment across the study treatment groups within the individual studies and pooled data.

Among the pooled groups, 27.8% and 35.5% of rezafungin and caspofungin subjects, respectively, switched from IV to oral step-down therapy, most frequently on Day 4–6 (54.8% and 47.5%, respectively), on Day 7–9 (21.4% and 16.9%, respectively), and on Day 10–12 (7.1% and 22.0%, respectively).

Table 6. Study Drug Exposure – Safety Population

Exposure	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Duration of study drug exposure (days)							
IV and oral therapy combined							
n	81	53	68	98	98	151	166
Mean	13.0	13.0	13.8	12.4	13.8	12.6	13.8
SD	6.50	6.03	6.77	6.46	6.16	6.29	6.40
Median	14.0	14.0	14.0	14.0	14.0	14.0	14.0
25th–75th percentile	11.0–15.0	13.0–14.0	12.0–16.0	7.0–14.0	13.0–15.0	9.0–14.0	13.0–15.0
Min, Max	1, 28	1, 28	1, 28	1, 28	1, 28	1, 28	1, 28
IV therapy							
n	81	53	68	98	98	151	166
Mean	11.6	11.6	11.9	11.1	12.3	11.3	12.1
SD	6.38	5.34	6.63	6.07	5.74	5.81	6.11
Median	14.0	14.0	12.0	14.0	14.0	14.0	14.0
25th–75th percentile	8.0–14.0	8.0–14.0	8.0–15.0	6.0–14.0	8.0–15.0	8.0–14.0	8.0–15.0
Min, Max	1, 28	1, 22	1, 28	1, 28	1, 28	1, 28	1, 28
Oral therapy [a]							
n	23	16	24	24	34	40	58
Mean	8.5	8.6	8.5	9.9	9.4	9.4	9.0
SD	4.78	5.86	3.36	4.29	5.10	4.95	4.45

Exposure	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Median	7.0	8.0	9.0	10.0	10.0	10.0	9.0
25th–75th percentile	6.0–11.0	3.5–11.0	7.0–10.5	7.0–11.0	5.0–12.0	6.5–11.0	6.0–11.0
Min, Max	2, 25	2, 22	2, 18	1, 24	2, 21	1, 24	2, 21
Distribution of study drug exposure duration (days)							
IV and oral therapy combined							
1–7	17 (21.0)	9 (17.0)	13 (19.1)	25 (25.5)	17 (17.3)	34 (22.5)	30 (18.1)
8–14	42 (51.9)	32 (60.4)	34 (50.0)	53 (54.1)	52 (53.1)	85 (56.3)	86 (51.8)
15–28	22 (27.2)	12 (22.6)	21 (30.9)	20 (20.4)	29 (29.6)	32 (21.2)	50 (30.1)
>28	0	0	0	0	0	0	0
IV therapy							
1–7	20 (24.7)	9 (17.0)	15 (22.1)	27 (27.6)	19 (19.4)	36 (23.8)	34 (20.5)
8–14	42 (51.9)	34 (64.2)	35 (51.5)	54 (55.1)	52 (53.1)	88 (58.3)	87 (52.4)
15–28	19 (23.5)	10 (18.9)	18 (26.5)	17 (17.3)	27 (27.6)	27 (17.9)	45 (27.1)
>28	0	0	0	0	0	0	0
Oral therapy [b]	24 (29.6)	17 (32.1)	24 (35.3)	25 (25.5)	35 (35.7)	42 (27.8)	59 (35.5)
1–3	3 (12.5)	4 (23.5)	3 (12.5)	1 (4.0)	6 (17.1)	5 (11.9)	9 (15.3)
4–7	9 (37.5)	4 (23.5)	6 (25.0)	7 (28.0)	8 (22.9)	11 (26.2)	14 (23.7)
8–14	10 (41.7)	6 (35.3)	14 (58.3)	14 (56.0)	13 (37.1)	20 (47.6)	27 (45.8)
15–28	1 (4.2)	2 (11.8)	1 (4.2)	2 (8.0)	7 (20.0)	4 (9.5)	8 (13.6)
>28	0	0	0	0	0	0	0
Unknown	1 (4.2)	1 (5.9)	0	1 (4.0)	1 (2.9)	2 (4.8)	1 (1.7)

Adjusted disposition tables:

In the Integrated Summary of Safety document, the applicant reports that they noticed discrepancies between the TEAEs listed as leading to discontinuation versus the CRF descriptions.

They found 37 instances for Rezafungin and 25 for Caspofungin in which there was a TEAE with outcome of fatal or resulted in discontinuation, which was not reported as discontinuation in the disposition data. They then adjusted the disposition tables and provide them as a post hoc 'adjusted disposition table', adjustments in bold in table 8 below.

Table 8. Adjusted Subject Disposition – Safety Population

Disposition Reason, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin (Group 1: 400/400 mg) (N = 81)	Rezafungin (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
At least 1 TEAE leading to study discontinuation	**13 (16.0)**	**6 (11.3)**	**13 (19.1)**	**26 (26.5)**	**25 (25.5)**	**32 (21.2)**	**38 (22.9)**
Completed study	**57 (70.4)**	41 (77.4)	51 (75.0)	59 (60.2)	59 (60.2)	100 (66.2)	110 (66.3)
Discontinued study early	**24 (29.6)**	12 (22.6)	17 (25.0)	39 (39.8)	39 (39.8)	51 (33.8)	56 (33.7)
Adverse event	**1 (1.2)**	0	**1 (1.5)**	**2 (2.0)**	**2 (2.0)**	**2 (1.3)**	3 (1.8)
Death	11 (13.6)	6 (11.3)	**11 (16.2)**	22 (22.4)	**22 (22.4)**	28 (18.5)	33 (19.9)
Lost to follow-up	4 (4.9)	3 (5.7)	1 (1.5)	4 (4.1)	5 (5.1)	7 (4.6)	6 (3.6)
Non-compliance	1 (1.2)	1 (1.9)	0	0	0	1 (0.7)	0
Physician's decision	2 (2.5)	0	1 (1.5)	0	0	0	1 (0.6)
Withdrawal by subject	4 (4.9)	1 (1.9)	1 (1.5)	6 (6.1)	7 (7.1)	7 (4.6)	8 (4.8)
Other	1 (1.2)	1 (1.9)	2 (2.9)	7 (7.1)	3 (3.1)	8 (5.3)	5 (3.0)

ISS = Integrated Summary of Safety; N = number of subjects; n = number of subjects in the category; TEAE = treatment-emergent adverse event.
Note: **bold** text denotes changes compared with Table 7, with only the adverse event and death categories with revised data

Regarding the adjusted disposition data, that arose from discrepancies being noticed after DLP, is it understood that the main impact of these discrepancies was that additional AEs that results in treatment interruption or discontinuation were identified, which meant that the disposition data had to be updated. However, in Section 3.3.1.1 mentions that AE CRF data was also updated. No additional AEs or SAEs were identified.

Overall, the numbers exposed are not large. In terms of the proposed posology, a total of 316 subjects has been enrolled across the development programme (76 subjects in Phase 1,134 patients in Phase 2, 98 patients in Phase 3, and an additional 8 patients in the expanded access programme) at or above the dose and duration for the proposed commercial dose.

There are no clinical trial data for treatment duration > 28 days, however the posology makes clear that treatment for more than 28 days is not anticipated. Further safety data will be available from the prophylactic indication (not submitted in this application). Overall, the numbers can be considered adequate for short term use only, as per the posology, provided no signals emerge from the data.

2.6.8.2. Adverse events

No subjects in the Phase 1 studies administered rezafungin experienced TEAEs at an incidence of ≥30% (a higher threshold than that used for the Phase 2 STRIVE and Phase 3 ReSTORE pooled data, as the number of subjects within the individual Phase 1 studies was small in comparison and the 5% threshold used in the pooled data would result in AEs occurring in 1 or 2 subjects presented as "common").

The most common occurring AEs in the pooled data from the Phase 2 and Phase 3 studies (occurring in ≥10% of either pooled treatment group) PTs were hypokalaemia (14.6% and 10.2% subjects in the pooled rezafungin and caspofungin groups, respectively), pyrexia (11.9% and 6.6%, respectively), and diarrhoea (11.3% and 10.2%, respectively). The incidence patterns of TEAEs were similar across the study treatment groups within the individual studies and pooled data.

Treatment-emergent AEs occurring in ≥5% of subjects in either pooled treatment group are summarised in Table 8 for the Safety Population from the Phase 2 STRIVE and Phase 3 ReSTORE studies.

Table 8. Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects in Either Pooled Treatment Group by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Number of subjects with at least one TEAE [a]	69 (85.2)	49 (92.5)	55 (80.9)	89 (90.8)	83 (84.7)	138 (91.4)	138 (83.1)
Infections and infestations							
Pneumonia	6 (7.4)	2 (3.8)	4 (5.9)	10 (10.2)	3 (3.1)	12 (7.9)	7 (4.2)
Septic shock	8 (9.9)	1 (1.9)	3 (4.4)	10 (10.2)	9 (9.2)	11 (7.3)	12 (7.2)
Sepsis	1 (1.2)	4 (7.5)	4 (5.9)	6 (6.1)	4 (4.1)	10 (6.6)	8 (4.8)
Urinary tract infection	3 (3.7)	1 (1.9)	3 (4.4)	4 (4.1)	6 (6.1)	5 (3.3)	9 (5.4)
Gastrointestinal disorders							
Diarrhoea	7 (8.6)	11 (20.8)	10 (14.7)	6 (6.1)	7 (7.1)	17 (11.3)	17 (10.2)
Vomiting	6 (7.4)	8 (15.1)	5 (7.4)	6 (6.1)	2 (2.0)	14 (9.3)	7 (4.2)
Nausea	4 (4.9)	8 (15.1)	6 (8.8)	5 (5.1)	2 (2.0)	13 (8.6)	8 (4.8)
Abdominal pain	5 (6.2)	6 (11.3)	5 (7.4)	5 (5.1)	4 (4.1)	11 (7.3)	9 (5.4)
Constipation	3 (3.7)	3 (5.7)	5 (7.4)	5 (5.1)	3 (3.1)	8 (5.3)	8 (4.8)
Metabolism and nutrition disorders							
Hypokalaemia	13 (16.0)	9 (17.0)	8 (11.8)	13 (13.3)	9 (9.2)	22 (14.6)	17 (10.2)
Hypomagnesaemia	1 (1.2)	5 (9.4)	2 (2.9)	7 (7.1)	3 (3.1)	12 (7.9)	5 (3.0)
Hypophosphataemia	3 (3.7)	3 (5.7)	1 (1.5)	5 (5.1)	4 (4.1)	8 (5.3)	5 (3.0)
Hyperkalaemia	0 (0.0)	1 (1.9)	3 (4.4)	2 (2.0)	6 (6.1)	3 (2.0)	9 (5.4)

System Organ Class Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
General disorders and administration site conditions							
Pyrexia	9 (11.1)	4 (7.5)	6 (8.8)	14 (14.3)	5 (5.1)	18 (11.9)	11 (6.6)
Respiratory, thoracic and mediastinal disorders							
Pleural effusion	5 (6.2)	0 (0.0)	6 (8.8)	3 (3.1)	4 (4.1)	3 (2.0)	10 (6.0)
Blood and lymphatic system disorders							
Anaemia	6 (7.4)	6 (11.3)	4 (5.9)	9 (9.2)	9 (9.2)	15 (9.9)	13 (7.8)
Vascular disorders							
Hypotension	6 (7.4)	2 (3.8)	4 (5.9)	5 (5.1)	6 (6.1)	7 (4.6)	10 (6.0)
Renal and urinary disorders							
Acute kidney injury	4 (4.9)	3 (5.7)	3 (4.4)	3 (3.1)	8 (8.2)	6 (4.0)	11 (6.6)

MedDRA: Medical Dictionary for Regulatory Activities; N: Number of subjects; n: Number of subjects in the category; PT: Preferred Term; SOC: System Organ Class; TEAE: Treatment-emergent adverse event.
Note: A TEAE is defined as an AE that occurs during or after study drug administration and up through the follow-up visit. A subject with multiple adverse events within an SOC or PT was counted only once. SOCs and PTs within SOC were sorted by descending frequency in the pooled rezafungin for injection column. Percentages were calculated using the total number of subjects in each treatment group (N) as the denominator. MedDRA Version 23.0 was used for reporting adverse events.
a. Row reports all subjects with at least one TEAE.
Source: ISS Table 2.2.1, ISS Table 2.5.1

It was agreed that only those AE with an incidence above 30%, due to the low number patients included in the Phase 1 studies, are considered, and no SAE were mentioned in the Phase 1 clinical studies. The most common AE in the Phase 2 (with an incidence above 5%) were by descending frequency hypokalaemia, pyrexia, diarrhoea, anemia, vomiting, nausea, pneumonia, hypomagnesemia, septic shock, abdominal pain, sepsis, constipation and hypophosphatemia. All AE belonging to the SOC Infections and infestations were higher in the rezafungin group with the exception of urinary tract infection.

Of note a class related AE related with the echinocandins class is hyperkalaemia, not found with rezafungin.

There are higher rates of AEs overall in the rezafungin pool than in the caspofungin pool (92.1% v 83.1%), as well as drug related TEAEs (14.3% v 10.8%) and SAEs (55% v 48.8%). Serious adverse events, deaths, and other significant events

2.6.8.3. Serious adverse event/deaths/other significant events

- Serious Adverse Events (SAE)

There were no SAEs in the Phase 1 studies in subjects receiving rezafungin.

Among the pooled groups in the Phase 2 STRIVE and Phase 3 ReSTORE studies, SAEs occurred in 55.0% of subjects in the rezafungin group, and 48.8% of subjects in the caspofungin group. The most common PT was septic shock (occurring in 6% of subjects in both treatment groups of the pooled data); other PTs occurred in ≤3.6% of subjects in either pooled treatment group.

Among the pooled groups, SAEs related to study drug occurred in 2.0% of subjects in the rezafungin group, and 3.0% of subjects in the caspofungin group. No PT occurred in more than one subject across the study treatment groups within the individual studies and pooled data.

There were a total of four potentially related SAEs in the rezafungin group, 1 in the Phase 2 STRIVE Group 1 (400/400 mg) and three in the 400/200 mg dose group across the two studies.

The related SAE in the 400/400 mg group in the Phase 2 STRIVE study was atrial flutter associated with ongoing Day 3 infusions of study drug, which was a saline placebo infusion for those in the rezafungin group. The other 3 related SAEs in the rezafungin 400/200 mg dose group were first-degree atrioventricular block (discovered on routine ECG at the end of treatment; the subject was asymptomatic but required delayed discharge to investigate the diagnosis, with an ECG repeated several days later and found to be normal, followed by subject discharge), infusion-related reaction, and urticaria. The SAEs of atrial flutter and infusion-related reaction were associated with ongoing Day 3 infusions of study drug, which was a saline placebo infusion for those in the rezafungin arm. The SAE of urticaria was deemed by the Investigator to be related to oral study drug (urticaria developed following administration of oral study medication [which is the placebo for subjects in the rezafungin arm] and resulted in hospitalisation being prolonged).

The five related SAEs for caspofungin in the Phase 2 STRIVE study and Phase 3 ReSTORE study were ventricular tachycardia, rectal haemorrhage (associated with oral fluconazole study drug), hypertransaminesemia, liver injury, and anaphylactic shock.

Table 9. Serious Adverse Events Related to Study Drug by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Number of subjects with at least one related serious adverse event	1 (1.2)	1 (1.9)	2 (2.9)	2 (2.0)	3 (3.1)	3 (2.0)	5 (3.0)
Cardiac disorders	1 (1.2)	1 (1.9)	1 (1.5)	0	0	1 (0.7)	1 (0.6)
Atrioventricular block first-degree	0	1 (1.9)	0	0	0	1 (0.7)	0
Ventricular tachycardia	0	0	1 (1.5)	0	0	0	1 (0.6)
Atrial flutter	1 (1.2)	0	0	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	1 (1.0)	0	1 (0.7)	0
Infusion-related reaction	0	0	0	1 (1.0)	0	1 (0.7)	0
Skin and subcutaneous tissue disorders	0	0	0	1 (1.0)	0	1 (0.7)	0
Urticaria	0	0	0	1 (1.0)	0	1 (0.7)	0
Hepatobiliary disorders	0	0	0	0	2 (2.0)	0	2 (1.2)
Hypertransaminasaemia	0	0	0	0	1 (1.0)	0	1 (0.6)
Liver injury	0	0	0	0	1 (1.0)	0	1 (0.6)
Gastrointestinal disorders	0	0	1 (1.5)	0	0	0	1 (0.6)
Rectal haemorrhage	0	0	1 (1.5)	0	0	0	1 (0.6)
Immune system disorders	0	0	0	0	1 (1.0)	0	1 (0.6)
Anaphylactic shock	0	0	0	0	1 (1.0)	0	1 (0.6)

System Organ Class Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)

MedDRA: Medical Dictionary for Regulatory Activities; N: Number of subjects; n: umber of subjects in the category; PT: Preferred Term; SOC: System Organ Class.
Note: A subject with multiple adverse events within an SOC or PT was counted only once. SOCs and PTs within SOC were sorted by descending frequency in the pooled rezafungin for injection column. Percentages were calculated using the total number of subjects in each treatment group (N) as the denominator. MedDRA Version 23.0 was used for reporting adverse events.
Source: Data on File.

The other two SAE were an infusion-related reaction, and urticaria (was deemed by the Investigator to be related to oral study drug).

- Deaths

There were no subject deaths in any of the Phase 1 studies.

Among the pooled groups in the Phase 2 STRIVE and Phase 3 ReSTORE studies, SAEs resulting in death occurred in 23.2% of subjects in the rezafungin treated group, and 24.1% of subjects in the caspofungin group. The most common SOC was Infections and infestations (9.3% and 14.5% subjects in the rezafungin and caspofungin groups, respectively); all other SOCs occurred in ≤5.4% of subjects in either group. The most common PT was septic shock (5.3% and 6.0% subjects, respectively); other PTs occurred in ≤3.3% of subjects in either pooled treatment group. The incidence pattern of SAEs resulting in death was similar across the study treatment groups within the individual studies and pooled data.

Table 10. Serious Adverse Events Resulting in Death by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Number of subjects with at least one serious adverse event resulting in death	14 (17.3)	6 (11.3)	15 (22.1)	29 (29.6)	25 (25.5)	35 (23.2)	40 (24.1)
Infections and infestations	10 (12.3)	2 (3.8)	7 (10.3)	12 (12.2)	17 (17.3)	14 (9.3)	24 (14.5)
Septic shock	8 (9.9)	1 (1.9)	2 (2.9)	7 (7.1)	8 (8.2)	8 (5.3)	10 (6.0)
Sepsis	0	1 (1.9)	1 (1.5)	2 (2.0)	2 (2.0)	3 (2.0)	3 (1.8)
Candida sepsis	0	0	1 (1.5)	1 (1.0)	0	1 (0.7)	1 (0.6)
Bronchopulmonary aspergillosis	0	0	0	1 (1.0)	0	1 (0.7)	0
Catheter bacteraemia	0	0	0	1 (1.0)	0	1 (0.7)	0
Device-related sepsis	0	0	0	1 (1.0)	0	1 (0.7)	0
Pneumonia	0	0	0	1 (1.0)	0	1 (0.7)	0
Pneumonia pseudomonal	0	0	0	1 (1.0)	0	1 (0.7)	0
COVID-19 pneumonia	0	0	0	0	2 (2.0)	0	2 (1.2)
Acinetobacter sepsis	0	0	0	0	1 (1.0)	0	1 (0.6)
Bacterial sepsis	0	0	0	0	1 (1.0)	0	1 (0.6)
Bronchitis	0	0	1 (1.5)	0	0	0	1 (0.6)
COVID-19	0	0	0	0	1 (1.0)	0	1 (0.6)
Endocarditis *Candida*	0	0	1 (1.5)	0	0	0	1 (0.6)
Klebsiella sepsis	0	0	0	0	1 (1.0)	0	1 (0.6)

System Organ Class Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Pneumonia *Klebsiella*	0	0	0	0	1 (1.0)	0	1 (0.6)
Pulmonary sepsis	0	0	1 (1.5)	0	0	0	1 (0.6)
Peritonitis	1 (1.2)	0	0	0	0	0	0
Systemic *Candida*	1 (1.2)	0	0	0	0	0	0
Cardiac disorders	0	1 (1.9)	2 (2.9)	5 (5.1)	2 (2.0)	6 (4.0)	4 (2.4)
Cardiac arrest	0	1 (1.9)	1 (1.5)	2 (2.0)	0	3 (2.0)	1 (0.6)
Cardio-respiratory arrest	0	0	0	1 (1.0)	1 (1.0)	1 (0.7)	1 (0.6)
Ventricular tachycardia	0	0	0	1 (1.0)	1 (1.0)	1 (0.7)	1 (0.6)
Cardiopulmonary failure	0	0	0	1 (1.0)	0	1 (0.7)	0
Myocarditis	0	0	0	1 (1.0)	0	1 (0.7)	0
Cardiac failure	0	0	1 (1.5)	0	0	0	1 (0.6)
General disorders and administration site conditions	2 (2.5)	0	1 (1.5)	6 (6.1)	2 (2.0)	6 (4.0)	3 (1.8)
Multiple organ dysfunction syndrome	2 (2.5)	0	1 (1.5)	5 (5.1)	2 (2.0)	5 (3.3)	3 (1.8)
Death	0	0	0	1 (1.0)	0	1 (0.7)	0
Respiratory, thoracic and mediastinal disorders	0	2 (3.8)	5 (7.4)	3 (3.1)	4 (4.1)	5 (3.3)	9 (5.4)
Respiratory failure	0	1 (1.9)	1 (1.5)	0	2 (2.0)	1 (0.7)	3 (1.8)
Acute respiratory distress syndrome	0	0	1 (1.5)	1 (1.0)	0	1 (0.7)	1 (0.6)
Acute respiratory failure	0	0	1 (1.5)	1 (1.0)	0	1 (0.7)	1 (0.6)
Hypoxia	0	0	0	1 (1.0)	0	1 (0.7)	0

System Organ Class Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Pneumonia aspiration	0	1 (1.9)	0	0	0	1 (0.7)	0
Aspiration	0	0	1 (1.5)	0	0	0	1 (0.6)
Pleural effusion	0	0	0	0	1 (1.0)	0	1 (0.6)
Pneumonia lipoid	0	0	0	0	1 (1.0)	0	1 (0.6)
Pneumothorax	0	0	1 (1.5)	0	0	0	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.5)	1 (1.9)	1 (1.5)	4 (4.1)	2 (2.0)	5 (3.3)	3 (1.8)
Malignant neoplasm progression	2 (2.5)	0	1 (1.5)	1 (1.0)	0	1 (0.7)	1 (0.6)
Neoplasm malignant	0	1 (1.9)	0	0	1 (1.0)	1 (0.7)	1 (0.6)
Gastric cancer stage IV	0	0	0	1 (1.0)	0	1 (0.7)	0
Lymphoma	0	0	0	1 (1.0)	0	1 (0.7)	0
Squamous cell carcinoma of the tongue	0	0	0	1 (1.0)	0	1 (0.7)	0
Metastases to central nervous system	0	0	0	0	1 (1.0)	0	1 (0.6)
Vascular disorders	0	0	0	2 (2.0)	0	2 (1.3)	0
Shock	0	0	0	2 (2.0)	0	2 (1.3)	0
Death NOS	0	0	0	1 (1.0)	0	1 (0.7)	0
Death NOS	0	0	0	1 (1.0)	0	1 (0.7)	0
Nervous system disorders	1 (1.2)	1 (1.9)	0	0	0	1 (0.7)	0
Neurodegenerative disorder	0	1 (1.9)	0	0	0	1 (0.7)	0

System Organ Class Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Encephalopathy	1 (1.2)	0	0	0	0	0	0
Gastrointestinal disorders	0	0	0	0	2 (2.0)	0	2 (1.2)
Intestinal ischaemia	0	0	0	0	1 (1.0)	0	1 (0.6)
Intra-abdominal haemorrhage	0	0	0	0	1 (1.0)	0	1 (0.6)
Blood and lymphatic system disorders	1 (1.2)	0	0	0	0	0	0
Disseminated intravascular coagulation	1 (1.2)	0	0	0	0	0	0

MedDRA: Medical Dictionary for Regulatory Activities; N: Number of subjects; n: Number of subjects in the category; NOS: Not otherwise specified; PT: Preferred Term; SOC: System Organ Class.
Note: A subject with multiple adverse events within an SOC or PT was counted only once. SOCs and PTs within SOC were sorted by descending frequency in the pooled rezafungin for injection column. Percentages were calculated using the total number of subjects in each treatment group (N) as the denominator. MedDRA Version 23.0 was used for reporting adverse events.
Source: ISS Table 2.10.

- Adverse Events of Special Interest (AESIs)

An adverse event of special interest was defined per protocol as any event that may represent intolerance of the intravenous infusion of study drug, phototoxicity, ataxia, neuropathy, or tremor. These were based on either class effects of the drug or data from the non-clinical studies.

There were seven subjects with AESIs in the Phase 1 studies receiving rezafungin:

- In the CD101.IV.1.02 (MAD) study, 4 subjects in the rezafungin group experienced mild, transient infusion reactions, characterised by flushing, feeling hot, nausea, and chest discomfort. These infusion reactions were associated primarily with the 400 mg dose cohort and were most common with the third dose. In general, these reactions occurred within minutes of infusion initiation and disappeared within minutes without interruption or discontinuation of the study drug infusion. One subject in the 400 mg dose cohort had an

infusion reaction with dose 2 and dose 3. No intervention was required for the symptoms and there were no sequelae.

- In the CD101.IV.1.07 (photosensitivity) study one subject experienced an infusion-related reaction that was non-serious, of moderate intensity considered related to rezafungin and resulted in the subject withdrawal from the study. The Investigator and the Sponsor assessed the AE of mild vasovagal reaction (PT: presyncope) as not related to rezafungin as the event occurred prior to study drug administration. The Investigator and the Sponsor assessed the AE of mild allergic reaction (PT: hypersensitivity) as related to rezafungin. The Sponsor assessed the symptoms of shortness of breath and facial flushing during study drug infusion as being consistent with an infusion reaction and not hypersensitivity. The event was considered expected for rezafungin.

- In the CD101.IV.1.09 (DDI) study one subject receiving the rezafungin, tacrolimus and repaglinide regimen experienced tremors of mild intensity that resolved 1 hour and 5 minutes after onset. This subject also experienced TEAEs of mild anxiety, mild sensation of warmth and mild dizziness in parallel. All events resolved spontaneously and did not recur thereafter. The investigator considered the tremor related to tacrolimus but not related to rezafungin or repaglinide. Tremor is a labelled effect of tacrolimus.

In the Phase 2 STRIVE and Phase 3 ReSTORE studies, AESIs occurred in 10 (6.6%) of subjects in the pooled rezafungin group and 5 (3.0%) of subjects in the pooled caspofungin group.

The adverse events of special interest are discussed below in four categories, infusion-related reactions, tremor, neuropathy and phototoxicity.

Infusion-related Reactions

Infusion-related reactions occurred in five subjects in the Phase 2 STRIVE and Phase 3 ReSTORE pooled groups, 4 (2.6%) of whom were in the rezafungin group (2 in subjects receiving saline placebo infusion), and 1 (0.6%) in the caspofungin group (anaphylactic shock during caspofungin infusion on Day 3).

Phototoxicity

A single phototoxicity related reaction occurred in one subject who received rezafungin in the Phase 2 STRIVE study, this subject experienced mild sunburn following prolonged exposure to the sun. There were no phototoxicity related events in the Phase 3 ReSTORE study.

Tremor

Within the subordinate Preferred Terms categories of the SOC of "Nervous system disorders", only "Tremor" occurs in the rezafungin arms at an incidence that is apparently higher (4/151) than in the caspofungin arms (0/166).

The Causality Assessments of these four AEs of "Tremor" were assessed by an independent neurologist.

1. The AE should have been reported as either "unwitnessed seizure and post-ictal neurological state, attributable to recent cerebral infarction" or "witnessed seizure, attributable to recent cerebral infarction" definitely not related to rezafungin treatment (Phase 2 STRIVE)

2. The AE reported as "fluid shifts with the use of diuretics" is possibly related to treatment with rezafungin, which may have contributed to unreported electrolyte abnormalities, based on class effects of echinocandins (Phase 2 STRIVE)

3. The AE of "hypokalaemia" is definitely related to rezafungin treatment, based on class effects of echinocandins (Phase 3 ReSTORE)

4. The AE of "hypocalcaemia" is definitely attributable to tumour lysis syndrome, caused by chemotherapy for lymphoma, and definitely not related to rezafungin treatment (Phase 3 ReSTORE) Secondary to an electrolyte imbalance which was deemed as secondary to rezafungin treatment only 2 are definitely (Phase 3 ReSTORE) or possibly (Phase 2 STRIVE) related to rezafungin treatment. These AEs were both mild in intensity, and were easily treated by correction of serum electrolytes, or resolved without treatment.

Based on the independent neurologist's review regarding the causality it was concluded that of these four cases, only two are definitely or possibly related to rezafungin treatment. All four AEs were mild in intensity, and were easily treated by correction of serum electrolytes, or resolved without treatment.

Considering the preclinical signal of tremors as well as phospholipidosis in sensory ganglia and peripheral nerves and given that there are 5 events of tremor reported in rezafungin treated patients v none in caspofungin, further monitoring for this as a potential AE is required.

It is agreed that in 4 of the 5 cases of tremor reported with rezafungin there are electrolyte disturbances (hypokalaemia, hypocalcaemia), or baseline neurological conditions, or concomitant medication that might cause tremor and it is also agreed that the tremors in all cases were mild and did resolve. There is at least 1 of the 5 cases where an alternative explanation was not obvious- in particular, a subject reported non-serious mild tremor of upper limbs 3 days after the last dose- considered related by the investigator. Two of the 5 cases were reported as related to rezafungin by the investigators.

Given the confounders, it is difficult to conclude if rezafungin may have played a role with tremor in these cases. It is also the case that the safety database is limited and the numbers exposed may not yet be sufficient to fully evaluate this risk.

Neuropathy

Incidence of neuropathy (all neuropathy PTs, plus ICU weakness) was higher in the caspofungin treatment group (4 subjects versus 2 subjects in the rezafungin group). Of the 81 high dose (400/400 mg) rezafungin subjects, there were no reported events of neuropathy.

Table 11. Adverse Events of Special Interest by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Number of subjects with at least one adverse event of special interest	2 (2.5)	4 (7.5)	2 (2.9)	6 (6.1)	3 (3.1)	10 (6.6)	5 (3.0)
Nervous system disorders	0	4 (7.5)	2 (2.9)	2 (2.0)	2 (2.0)	6 (4.0)	4 (2.4)
Tremor	0	2 (3.8)	0	2 (2.0)	0	4 (2.6)	0
Intensive care unit acquired weakness	0	1 (1.9)	1 (1.5)	0	0	1 (0.7)	1 (0.6)
Peroneal nerve palsy	0	1 (1.9)	0	0	0	1 (0.7)	0
Polyneuropathy	0	0	1 (1.5)	0	1 (1.0)	0	2 (1.2)
Neuropathy peripheral	0	0	0	0	1 (1.0)	0	1 (0.6)
Injury, poisoning and procedural complications	2 (2.5)	0	0	3 (3.1)	0	3 (2.0)	0
Infusion-related reaction [a]	1 (1.2)	0	0	3 (3.1)	0	3 (2.0)	0
Sunburn	1 (1.2)	0	0	0	0	0	0
Immune system disorders	0	0	0	1 (1.0)	1 (1.0)	1 (0.7)	1 (0.6)
Infusion-related hypersensitivity reaction [a, b]	0	0	0	1 (1.0)	0	1 (0.7)	0
Anaphylactic shock	0	0	0	0	1 (1.0)	0	1 (0.6)
General disorders and administration site conditions	0	0	0	1 (1.0)	0	1 (0.7)	0
Adverse drug reaction [a, b]	0	0	0	1 (1.0)	0	1 (0.7)	0

MedDRA: Medical Dictionary for Regulatory Activities; N: Number of subjects; n: Number of subjects in the category; PT: Preferred Term; SOC: System Organ Class.
Note: An adverse event of special interest is defined per protocol as any event that may represent intolerance of the intravenous infusion of study drug, phototoxicity, ataxia, neuropathy, and tremors. A subject with multiple adverse events within an SOC or PT was counted only once. SOCs and PTs within SOC were sorted by descending frequency in the pooled rezafungin for injection column. Percentages were calculated using the total number of subjects in each treatment group (N) as the denominator. MedDRA Version 23.0 was used for reporting adverse events.

a. The infusion-related hypersensitivity reaction, adverse drug reaction, and one subject with infusion-related reactions occurred during administration of saline placebo.
b. The PT of infusion-related hypersensitivity reaction was reported as "rash and significant wheezing during study drug infusion" in a subject receiving saline placebo on Day 3. The PT of adverse drug reaction was a rash that occurred during study drug infusion (saline placebo) in the same subject on Day 4.

Source: ISS Table 2.11.

AEs were not analysed by organ system of syndrome in the Phase 1 studies.

2.6.8.4. Laboratory findings

There were no meaningful trends in post-baseline laboratory abnormalities or shifts from normal at baseline to outside the normal range post-baseline for any haematology, chemistry, or urinalysis parameters in the healthy subjects in any Phase 1 studies.

Phase 2 Strive and Phase 3 ReSTORE

Most subjects had normal renal and liver function at baseline, and no history of diabetes mellitus across all study treatment groups and pooled data.

Chemistry and Haematology Two-Grade Increases

Among the pooled groups, two-grade increases in chemistry and haematology laboratory values occurred in the rezafungin and caspofungin groups: creatinine increased (13.1% and 19.8% subjects, respectively), glucose increased (13.8% of subjects in both treatment groups), potassium decreased (11.0% and 7.5% subjects, respectively), and leukocytes increased (12.8% and 19.8% subjects, respectively).

Two-grade increases in liver enzymes were lower in the rezafungin compared to the caspofungin pooled group with increases in alanine aminotransferase (ALT) occurring in 2.7% versus 7.5% subjects, respectively; aspartate aminotransferase (AST) occurring in 4.2% versus 8.8% subjects, respectively; bilirubin occurring in 4.1% versus 8.1% subjects, respectively; and alkaline phosphatase (ALP) occurring in 5.0% versus 7.4% subjects, respectively.

The remaining two-grade increases occurred in <10% of subjects in either pooled treatment group.

Liver Enzyme Abnormalities

Table 12. Liver Laboratories Abnormalities at Any Time Post-Baseline – Safety Population

Category, n/N1 (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
ALT >3 × ULN	2/77 (2.6)	2/52 (3.8)	9/67 (13.4)	10/97 (10.3)	14/96 (14.6)	12/149 (8.1)	23/163 (14.1)
ALT >5 × ULN	1/77 (1.3)	0/52 (0.0)	3/67 (4.5)	2/97 (2.1)	7/96 (7.3)	2/149 (1.3)	10/163 (6.1)
ALT >8 × ULN	0/77 (0.0)	0/52 (0.0)	1/67 (1.5)	1/97 (1.0)	3/96 (3.1)	1/149 (0.7)	4/163 (2.5)
ALT >10 × ULN	0/77 (0.0)	0/52 (0.0)	0/67 (0.0)	1/97 (1.0)	3/96 (3.1)	1/149 (0.7)	3/163 (1.8)
AST >3 × ULN	6/76 (7.9)	2/52 (3.8)	10/67 (14.9)	16/97 (16.5)	17/96 (17.7)	18/149 (12.1)	27/163 (16.6)
AST >5 × ULN	0/76 (0.0)	1/52 (1.9)	1/67 (1.5)	5/97 (5.2)	9/96 (9.4)	6/149 (4.0)	10/163 (6.1)
AST >8 × ULN	0/76 (0.0)	0/52 (0.0)	1/67 (1.5)	3/97 (3.1)	5/96 (5.2)	3/149 (2.0)	6/163 (3.7)
AST >10 × ULN	0/76 (0.0)	0/52 (0.0)	1/67 (1.5)	1/97 (1.0)	4/96 (4.2)	1/149 (0.7)	5/163 (3.1)
ALT or AST >3 × ULN	8/77 (10.4)	4/52 (7.7)	13/67 (19.4)	19/97 (19.6)	22/96 (22.9)	23/149 (15.4)	35/163 (21.5)
ALT or AST >5 × ULN	1/77 (1.3)	1/52 (1.9)	3/67 (4.5)	6/97 (6.2)	12/96 (12.5)	7/149 (4.7)	15/163 (9.2)
ALT or AST >8 × ULN	0/77 (0.0)	0/52 (0.0)	1/67 (1.5)	4/97 (4.1)	5/96 (5.2)	4/149 (2.7)	6/163 (3.7)
ALT or AST >10 × ULN	0/77 (0.0)	0/52 (0.0)	1/67 (1.5)	2/97 (2.1)	4/96 (4.2)	2/149 (1.3)	5/163 (3.1)
TBL >1.5 × ULN	10/77 (13.0)	6/52 (11.5)	14/67 (20.9)	20/97 (20.6)	21/96 (21.9)	26/149 (17.4)	35/163 (21.5)
TBL >2 × ULN	8/77 (10.4)	5/52 (9.6)	10/67 (14.9)	15/97 (15.5)	14/96 (14.6)	20/149 (13.4)	24/163 (14.7)
ALP >2 × ULN	17/76 (22.4)	14/50 (28.0)	20/65 (30.8)	32/96 (33.3)	27/95 (28.4)	46/146 (31.5)	47/160 (29.4)
ALP >3 × ULN	8/76 (10.5)	4/50 (8.0)	14/65 (21.5)	15/96 (15.6)	14/95 (14.7)	19/146 (13.0)	28/160 (17.5)

Category, n/N1 (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
ALT or AST >3 x ULN and TBL >2 x ULN	4/77 (5.2)	1/52 (1.9)	1/67 (1.5)	8/97 (8.2)	3/96 (3.1)	9/149 (6.0)	4/163 (2.5)
ALT or AST >5 x ULN and TBL >2 x ULN	0/77 (0.0)	0/52 (0.0)	0/67 (0.0)	2/97 (2.1)	2/96 (2.1)	2/149 (1.3)	2/163 (1.2)
ALT or AST >8 x ULN and TBL >2 x ULN	0/77 (0.0)	0/52 (0.0)	0/67 (0.0)	1/97 (1.0)	1/96 (1.0)	1/149 (0.7)	1/163 (0.6)
ALT or AST >10 x ULN and TBL >2 x ULN	0/77 (0.0)	0/52 (0.0)	0/67 (0.0)	0/97 (0.0)	1/96 (1.0)	0/149 (0.0)	1/163 (0.6)
ALT or AST >3 x ULN and TBL >2.0 x ULN and ALP ≤2 xULN (potential Hy's Law)	1/76 (1.3)	0/50 (0.0)	0/65 (0.0)	6/96 (6.3)	0/95 (0.0)	6/146 (4.1)	0/160 (0.0)

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; N: Number of subjects; N1: Number of subjects having at least one post-baseline measurement of the specified laboratory parameter; n: Number of patients who meet the criterion at any time post-baseline; TBL: Total bilirubin; ULN: Upper limit of normal.
Note: For a combined criterion to be fulfilled, all conditions had to be fulfilled on the same lab measurement.
Source: ISS Table 3.4.1.

A total of 12/149 of the rezafungin pool had ALT > 3 X ULN, i.e. including those with higher grade rises (> 5ULN, >8ULN,>10ULN) and a total 18/49 of the rezafungin pool had AST > 3 X ULN, i.e. including with higher grade rises. These numbers are higher than those found with caspofungin.

Table 13. Potential Drug-Induced Liver Injury Adverse Events – Safety Population

Standardised MedDRA Query (SMQ) Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Number of subjects with at least one drug-induced liver injury adverse event	9 (11.1)	8 (15.1)	13 (19.1)	13 (13.3)	16 (16.3)	21 (13.9)	29 (17.5)
Cholestasis and jaundice of hepatic origin (SMQ, broad)	4 (4.9)	2 (3.8)	0	2 (2.0)	4 (4.1)	4 (2.6)	4 (2.4)
Cholestasis	2 (2.5)	2 (3.8)	0	1 (1.0)	3 (3.1)	3 (2.0)	3 (1.8)
Hyperbilirubinaemia	1 (1.2)	0	0	1 (1.0)	2 (2.0)	1 (0.7)	2 (1.2)
Drug-induced liver injury [a]	1 (1.2)	0	0	0	0	0	0
Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ, broad)	2 (2.5)	0	4 (5.9)	2 (2.0)	2 (2.0)	2 (1.3)	6 (3.6)
Hepatic steatosis	0	0	1 (1.5)	1 (1.0)	0	1 (0.7)	1 (0.6)
Hepatic lesion	0	0	0	1 (1.0)	0	1 (0.7)	0
Ascites	0	0	2 (2.9)	0	0	0	2 (1.2)
Hepatocellular injury	0	0	1 (1.5)	0	1 (1.0)	0	2 (1.2)
Liver injury	0	0	0	0	1 (1.0)	0	1 (0.6)
Drug-induced liver injury	1 (1.2)	0	0	0	0	0	0
Liver disorder	1 (1.2)	0	0	0	0	0	0
Hepatitis, non-infectious (SMQ, broad)	0	0	0	1 (1.0)	1 (1.0)	1 (0.7)	1 (0.6)

Standardised MedDRA Query (SMQ) Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Hepatitis	0	0	0	1 (1.0)	1 (1.0)	1 (0.7)	1 (0.6)
Liver related investigations, signs and symptoms (SMQ, broad)	6 (7.4)	6 (11.3)	11 (16.2)	9 (9.2)	10 (10.2)	15 (9.9)	21 (12.7)
Hypoalbuminaemia	1 (1.2)	4 (7.5)	1 (1.5)	2 (2.0)	2 (2.0)	6 (4.0)	3 (1.8)
Gamma-glutamyl transferase increased	0	0	1 (1.5)	2 (2.0)	2 (2.0)	2 (1.3)	3 (1.8)
Hypertransaminasaemia	0	0	0	2 (2.0)	2 (2.0)	2 (1.3)	2 (1.2)
Blood alkaline phosphatase increased	1 (1.2)	0	0	2 (2.0)	1 (1.0)	2 (1.3)	1 (0.6)
Blood bilirubin increased	0	0	1 (1.5)	1 (1.0)	2 (2.0)	1 (0.7)	3 (1.8)
Hepatic enzyme increased	1 (1.2)	0	3 (4.4)	1 (1.0)	0	1 (0.7)	3 (1.8)
Hyperbilirubinaemia	1 (1.2)	0	0	1 (1.0)	2 (2.0)	1 (0.7)	2 (1.2)
Hepatic function abnormal	1 (1.2)	0	0	1 (1.0)	1 (1.0)	1 (0.7)	1 (0.6)
Liver function test increased	0	1 (1.9)	1 (1.5)	0	0	1 (0.7)	1 (0.6)
Bilirubin conjugated increased	0	0	0	1 (1.0)	0	1 (0.7)	0
Hyperammonaemia	0	1 (1.9)	0	0	0	1 (0.7)	0
Ascites	0	0	2 (2.9)	0	0	0	2 (1.2)
Alanine aminotransferase increased	0	0	0	0	1 (1.0)	0	1 (0.6)
Aspartate aminotransferase increased	0	0	0	0	1 (1.0)	0	1 (0.6)
Haemorrhagic ascites	0	0	1 (1.5)	0	0	0	1 (0.6)
Hepatomegaly	0	0	1 (1.5)	0	0	0	1 (0.6)
Liver function test abnormal	1 (1.2)	0	1 (1.5)	0	0	0	1 (0.6)
Transaminases increased	0	0	1 (1.5)	0	0	0	1 (0.6)
Liver related coagulation and bleeding disturbances (SMQ, broad)	0	0	0	0	2 (2.0)	0	2 (1.2)
Hypofibrinogenaemia	0	0	0	0	1 (1.0)	0	1 (0.6)
International normalised ratio increased	0	0	0	0	1 (1.0)	0	1 (0.6)

MedDRA: Medical Dictionary for Regulatory Activities; N: Number of subjects; n: Number of subjects in the category; PT: Preferred Term; SMQ: Standardised MedDRA query.
Note: A subject with multiple adverse events within an SMQ or PT was counted only once. SMQs were presented alphabetically; PTs were sorted within SMQ by descending frequency in the pooled rezafungin for injection column. Percentages were calculated using the total number of subjects in each treatment group (N) as the denominator. MedDRA Version 23.0 was used for reporting adverse events.

a. Drug-induced liver injury in a Phase 2 STRIVE Group 1 subject was reported as hepatic toxicity to fluconazole. The subject received only a single dose of study drug before withdrawing. The event was reported as an SAE upon starting treatment with open-label fluconazole.

Source: ISS Table 2.12

There were 7 subjects (one in group 1 of the STRIVE Phase 2 study that had received 400mg/400mg, and six in the Phase 3 pool) in the rezafungin treatment group that met the laboratory criteria for Hy's Law (ALT or AST >3 × ULN and total bilirubin >2 × ULN and ALP ≤2 x ULN at the same visit; it's noteworthy that no subject on caspofungin met the laboratory criteria for Hy's Law.

All cases had confounding factors and the occurrence of a drug liver injury was unlikely.

The 7 cases of patients meeting Hy's law (in rezafungin treated patients only) deserved careful review and attention in terms of baseline LFTs, as well as details of the trend in LFT progression, confounders, final outcome.

It should also be noted that 10.6% of the rezafungin pool had baseline LFT elevation, which is lower than the caspofungin pool; 17.5% had baseline LFT elevation.

In 4/7 cases it seems that the subjects in fact met Hy's criteria at screening/baseline, and all 4 had alternative explanations for the liver dysfunction:-

-open abdominal wound and rhabdomyolysis
-ischaemic hepatitis, cholestatic hepatitis, multiple infections
-Child-Pugh Class B cirrhosis, sepsis
-Congested hepatopathy, severe autoimmune haemolytic anaemia, septic shock

For the remaining 3 cases while not meeting Hy's criteria at screening, there was some baseline hepatic dysfunction, and in all cases baseline bilirubin was raised ranging from 2.6-34.4 ULN, and there were also alternative explanations for the evolving liver dysfunction:

-Acute sickle cell crisis

-Left liver lobe gunshot injury

-Multiorgan dysfunction syndrome (MODS) and septic shock at enrolment, heart failure, respiratory failure, maxillofacial and mediastinal infections

It is also noted that in 2 of the cases there was no significant disimprovement in LFTs from baseline, with most or all of the parameters improving. In a third case while LFTs initially improved after rezafungin and later disimproved, at no point did LFTs worsen beyond baseline.

In terms of final outcome, 4 of the 7 patient that met Hy's law died and 3 recovered entirely from their liver dysfunction. For the 4 that died the narratives list the deaths as death by: Multi organ failure, sepsis, ARDS/Pneumonia, multiorgan failure/septic shock.

The occurrence of a drug liver injury was unlikely, but could not be ruled out.

It should also be noted that while the narratives mention that for many of the case Hy's criteria were reached on D8, the day of the second infusion, it was the case that the blood tests were collected prior to this second infusion, and not after. However, given the long half of rezafungin, it is still possible the liver toxicity might occur on D8 from dosing on D1.

The applicant provided Table 3.4.2, which shows that in the subjects with normal baseline liver function values, there were no cases of potential Hy's law in any patient, nor in any rezafungin patient.

Cidara Therapeutics, Inc.
Rezafungin for Injection/Integrated Summary of Safety

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Table 3.4.2
Liver Enzyme Abnormalities at any Time Post-Baseline - Subjects with Normal Baseline Value
Safety Population

	Phase 2 (STRIVE)			Phase 3 (ReSTORE)		Pooled	
Category	Rezafungin for Injection (Group 1: 400/400 mg) (N=81) n/N1 (%)	Rezafungin for Injection (Group 2: 400/200 mg) (N=53) n/N1 (%)	Caspofungin (70/50 mg) (N=68) n/N1 (%)	Rezafungin for Injection (400/200 mg) (N=98) n/N1 (%)	Caspofungin (70/50 mg) (N=98) n/N1 (%)	Rezafungin for Injection (400/200 mg) (N=151) n/N1 (%)	Caspofungin (70/50 mg) (N=166) n/N1 (%)
ALT >3x ULN	1/55 (1.8)	0/40 (0.0)	0/36 (0.0)	3/72 (4.2)	7/65 (10.8)	3/112 (2.7)	7/101 (6.9)
ALT >5x ULN	1/55 (1.8)	0/40 (0.0)	0/36 (0.0)	0/72 (0.0)	2/65 (3.1)	0/112 (0.0)	2/101 (2.0)
ALT >8x ULN	0/55 (0.0)	0/40 (0.0)	0/36 (0.0)	0/72 (0.0)	2/65 (3.1)	0/112 (0.0)	2/101 (2.0)
ALT >10x ULN	0/55 (0.0)	0/40 (0.0)	0/36 (0.0)	0/72 (0.0)	2/65 (3.1)	0/112 (0.0)	2/101 (2.0)
AST >3x ULN	2/50 (4.0)	0/32 (0.0)	4/35 (11.4)	5/61 (8.2)	6/65 (9.2)	5/93 (5.4)	10/100 (10.0)
AST >5x ULN	0/50 (0.0)	0/32 (0.0)	0/35 (0.0)	2/61 (3.3)	4/65 (6.2)	2/93 (2.2)	4/100 (4.0)
AST >8x ULN	0/50 (0.0)	0/32 (0.0)	0/35 (0.0)	1/61 (1.6)	4/65 (6.2)	1/93 (1.1)	4/100 (4.0)
AST >10x ULN	0/50 (0.0)	0/32 (0.0)	0/35 (0.0)	1/61 (1.6)	3/65 (4.6)	1/93 (1.1)	3/100 (3.0)
ALT or AST >3x ULN	3/62 (4.8)	0/43 (0.0)	4/44 (9.1)	6/78 (7.7)	10/76 (13.2)	6/121 (5.0)	14/120 (11.7)
ALT or AST >5x ULN	1/62 (1.6)	0/43 (0.0)	0/44 (0.0)	2/78 (2.6)	4/76 (5.3)	2/121 (1.7)	4/120 (3.3)
ALT or AST >8x ULN	0/62 (0.0)	0/43 (0.0)	0/44 (0.0)	1/78 (1.3)	4/76 (5.3)	1/121 (0.8)	4/120 (3.3)
ALT or AST >10x ULN	0/62 (0.0)	0/43 (0.0)	0/44 (0.0)	1/78 (1.3)	3/76 (3.9)	1/121 (0.8)	3/120 (2.5)
TBL >1.5x ULN	2/57 (3.5)	1/40 (2.5)	4/44 (9.1)	4/71 (5.6)	7/76 (9.2)	5/111 (4.5)	11/120 (9.2)
TBL >2x ULN	1/57 (1.8)	1/40 (2.5)	2/44 (4.5)	1/71 (1.4)	3/76 (3.9)	2/111 (1.8)	5/120 (4.2)
ALP >2x ULN	2/42 (4.8)	4/24 (16.7)	4/28 (14.3)	8/55 (14.5)	4/47 (8.5)	12/79 (15.2)	8/75 (10.7)
ALP >3x ULN	1/42 (2.4)	2/24 (8.3)	4/28 (14.3)	3/55 (5.5)	1/47 (2.1)	5/79 (6.3)	5/75 (6.7)
ALT or AST >3x ULN and TBL >2x ULN	0/50 (0.0)	0/35 (0.0)	1/31 (3.2)	1/58 (1.7)	1/64 (1.6)	1/93 (1.1)	2/95 (2.1)
ALT or AST >5x ULN and TBL >2x ULN	0/50 (0.0)	0/35 (0.0)	0/31 (0.0)	1/58 (1.7)	1/64 (1.6)	1/93 (1.1)	1/95 (1.1)
ALT or AST >8x ULN and TBL >2x ULN	0/50 (0.0)	0/35 (0.0)	0/31 (0.0)	0/58 (0.0)	1/64 (1.6)	0/93 (0.0)	1/95 (1.1)
ALT or AST >10x ULN and TBL >2x ULN	0/50 (0.0)	0/35 (0.0)	0/31 (0.0)	0/58 (0.0)	1/64 (1.6)	0/93 (0.0)	1/95 (1.1)
ALT or AST >3xULN & TBL > 2.0xULN & ALP <= 2xULN (potential Hy's Law)	0/30 (0.0)	0/18 (0.0)	0/17 (0.0)	0/36 (0.0)	0/37 (0.0)	0/54 (0.0)	0/54 (0.0)

- N1: Number of subjects having normal result at baseline and at least one post-baseline measurement of the specified laboratory
Percentages are calculated using N1.
- n: Number of patients who meet the criterion at any time post-baseline.
- For a combined criterion to be fulfilled, all conditions have to be fulfilled on the same lab measurement.
- AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, TBL: Total bilirubin, ALP = Alkaline phosphatase, ULN: Upper limit of normal.

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As can be seen from table 17 there were higher rates of all individual LFT parameter rises in the caspofungin group, with the exception of Alkaline Phosphatase which was comparable at 31.5% and 29.4%.

With the data provided a serious risk of hepatotoxicity cannot be ruled out. There were 7 patients meeting Hy's criteria after starting rezafungin, as well as at least separate 2 DILI AEs reported in rezafungin arms, versus none in the caspofungin arm.

Taking into account these data, a warning on hepatic effects was recommended to be added to section 4.4, in line with the existing information in other authorised products of the echinocandins class. Meanwhile, section 4.8 reflects that LFT abnormalities were common, which seems appropriate.

Nephrotoxicity

Among the pooled groups, nephrotoxicity at any time post-baseline occurred in 9.7% of subjects in the rezafungin, and 17.3% of subjects in the caspofungin group. This pattern was similar for the Phase 3 ReSTORE study, and for the Phase 2 STRIVE study between Group 2 (rezafungin 400/200 mg) versus caspofungin.

Table 14. Nephrotoxicity by Visit – Safety Population

Day, n/N1 (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Subjects with nephrotoxicity at any time post-baseline [a]	12/76 (15.8)	5/48 (10.4)	10/66 (15.2)	9/97 (9.3)	18/96 (18.8)	14/145 (9.7)	28/162 (17.3)
Day 1	0	0	0	1/22 (4.5)	0/13 (0.0)	1/22 (4.5)	0/13 (0.0)
Day 2	2/70 (2.9)	0/44 (0.0)	1/59 (1.7)	2/90 (2.2)	4/90 (4.4)	2/134 (1.5)	5/149 (3.4)
Day 4	7/67 (10.4)	1/40 (2.5)	2/55 (3.6)	2/78 (2.6)	9/84 (10.7)	3/118 (2.5)	11/139 (7.9)
Day 8	6/61 (9.8)	1/40 (2.5)	1/50 (2.0)	3/73 (4.1)	4/80 (5.0)	4/113 (3.5)	5/130 (3.8)
Day 14	2/30 (6.7)	0/17 (0.0)	3/24 (12.5)	1/26 (3.8)	2/31 (6.5)	1/43 (2.3)	5/55 (9.1)
Day 30	0	0	0	1/50 (2.0)	3/52 (5.8)	1/50 (2.0)	3/52 (5.8)
End of Therapy	4/65 (6.2)	2/43 (4.7)	7/58 (12.1)	4/78 (5.1)	4/87 (4.6)	6/121 (5.0)	11/145 (7.6)
Follow-up	3/45 (6.7)	2/27 (7.4)	3/42 (7.1)	1/55 (1.8)	7/53 (13.2)	3/82 (3.7)	10/95 (10.5)

N: Number of subjects; N1: Number of subjects with a baseline and post-baseline serum creatinine measurement at each visit; n: Number of patients who meet the criterion at any time post-baseline.
Note: Nephrotoxicity is defined as doubling of serum creatinine relative to baseline or an increase of 1 mg/dL in serum creatinine if baseline serum creatinine was above the upper limit of the normal range.
a. Denominator is the number of subjects having a baseline and at least one post-baseline serum creatinine measurement, including unscheduled visits.
Source: ISS Table 3.4.7.

Vital Signs, Physical Findings, And Other Observations Related To Safety

Phase 1 Studies

There were no clinically relevant treatment-related findings observed for vital signs measurements, ECGs, or physical examinations in any of the Phase 1 studies. In Study CD101.IV.1.06, rezafungin in single doses as high as to 1400 mg did not prolong the QTcF interval. There were no clinically significant findings in other cardiac parameters, including HR, PR interval, and QRS interval between rezafungin (600 mg and 1400 mg) and placebo.

Phase 2 Strive and Phase 3 ReSTORE

In the Phase 2 STRIVE and Phase 3 ReSTORE studies, potentially clinically significant vital sign measurements, had a similar incidence across the study treatment groups within the individual studies and pooled data with the following exceptions:

• Bradycardia (heart rate ≤50 bpm and decrease of ≥15 bpm) occurred in 6.8% and 13.6% of subjects in the pooled rezafungin and caspofungin groups, respectively. Tachycardia (heart rate ≥120 bpm and increase of ≥15 bpm) occurred in 20.9% and 28.4% of subjects, respectively.

• Increased systolic blood pressure (≥180 mmHg and increase of ≥20 mmHg) occurred in 32.7% of subjects in Phase 2 STRIVE rezafungin Group 2 compared to 21.5% of subjects in Group 1 and 18.2% of subjects in the caspofungin group.

• Temperature increased (>38°C and increase of ≥1°C) occurred in 25.4% of subjects in the Phase 2 STRIVE caspofungin group compared to 17.3% in the rezafungin Group 2.

Electrocardiograms

Effects on QT Interval and Other ECG Intervals (Study CD101.IV.1.06)

The effect of rezafungin on the QT interval and other ECG intervals was assessed in a Phase 1, single-centre, randomised, comparative study of the effect of SAD of rezafungin (n=12 at each dose level), a negative control (placebo; n=12), and a positive control (moxifloxacin 400 mg plus IV placebo; n=24) in healthy adult subjects.

A total of 60 subjects were enrolled and completed all treatments assigned.

The study assessed 2 rezafungin dose levels: 600 mg and 1400 mg. Doses for this study were selected to achieve relevant therapeutic and supratherapeutic exposures, respectively. The supratherapeutic dose was chosen to be within relevant human safety margins. Rezafungin was administered by IV infusion at 600 mg in 375 mL over 1.5 hours (± 5 minutes) followed by IV placebo infusion in 500 mL over 2 hours (± 5 minutes) to total 875 mL over 3.5 hours in cohort 1. Rezafungin was administered by IV infusion at 1400 mg divided into a 375 mL infusion over 1.5 hours (± 5 minutes) followed by a 500 mL infusion over 2 hours (± 5 minutes) to total 875 mL over 3.5 hours in cohort 2.

A single subject who received rezafungin 1400 mg, had 4 values of QTcF > 450 msec after a baseline QTcF of 444.7 msec.

No other subjects had elevated QTcF values and no values of ΔQTcF were > 30 msec for placebo or rezafungin.

The secondary endpoint, determination of mean ΔΔQTcF at each time point by dose, showed all 1-sided 95% upper bounds to be < 10 msec, thus supporting the conclusion of the primary analysis. The maximum value of mean ΔΔQTcF was -2.2 msec for rezafungin 1400 mg IV at 8 hours post-start of infusion, with an upper bound of 4.0 msec.

Phase 2 and Phase 3 studies

As the ECG was conducted at different timepoints in the Phase 2 STRIVE and Phase 3 ReSTORE studies, no integrated analysis was performed.

In the Phase 3 ReSTORE study, the percentage of subjects with a ≥500 msec QTcF on Day 1 was 6.0% and 4.8% in the rezafungin and caspofungin groups, respectively. Of these subjects with a Day 1 post-infusion elevated QTcF, 3 subjects in the rezafungin group and 1 subject in the caspofungin group had a baseline QTcF >500 msec (i.e., prior to study drug dosing). Those with a ≥60 msec Day 1 change from baseline in QTcF were 3.8% and 10.0% for rezafungin and caspofungin, respectively.

Based upon Data and Safety Monitoring Board feedback due to an imbalance of cardiovascular SOC events, an external cardiology consultant reviewed the cardiac safety for the Phase 3 ReSTORE study. There was an inconsistent or imprecise classification of cardiac safety endpoints which complicated evaluation of the incidence of cardiac SAEs in the Phase 3 ReSTORE study.

No integrative analyses as stated by the applicant was made regarding ECG abnormalities. Two SAE were arrhythmias: a atrial flutter in the 400/400mg (although with saline administration the event cannot be ruled

out as not rezafungin related due to is long ½ life) and a first degree AV block in the 400/200mg group. The true rate of cardiac abnormalities could not be determined.

Overall, it is agreed that rezafungin is not expected to have clinically important effects on cardiac conduction, and there were no cardiac safety issues observed in the rezafungin clinical development programme.

2.6.8.5. Safety in special populations

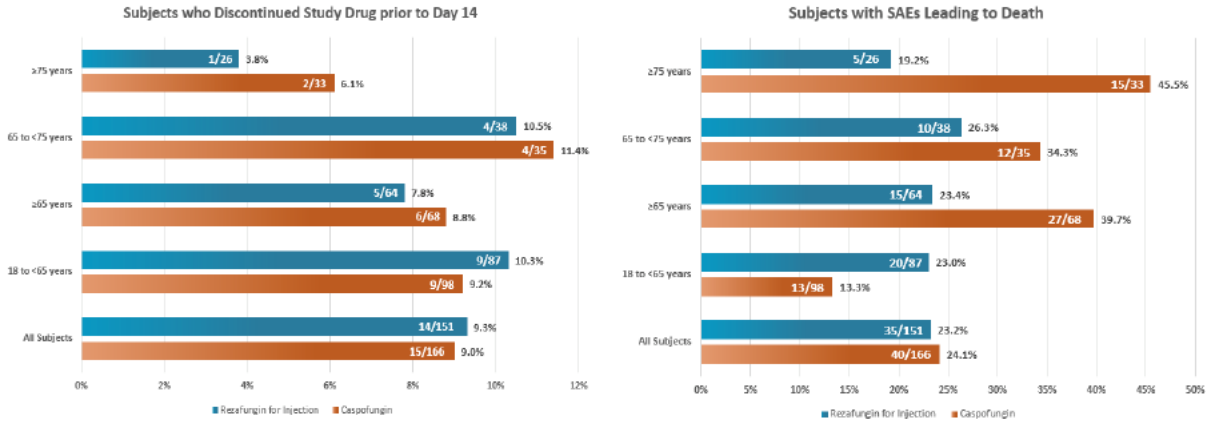
- Age

Among the pooled groups, the proportion of subjects <65 years of age with TEAEs was higher in the rezafungin group compared with the caspofungin group (90.8% versus 77.6%, respectively); the proportion was similar in subjects ≥65 years of age.

In subjects ≥65 years of age, the incidence of TEAEs leading to study discontinuation was 10.9% for the rezafungin treatment group compared with 27.9% for the caspofungin treatment group. A similar treatment difference was also observed for both age subgroups within the ≥65 years of age category. In the subgroup of subjects ≥75 years of age, in the rezafungin group (N=26), the incidence of SAEs leading to death was 19.2% compared with 45.5% for the caspofungin group (N=33).

For severe/Grade ≥3 TEAEs, the incidence was 46.2% versus 60.6%, respectively. There were no noteworthy differences by age group for vital signs, liver enzyme abnormalities, or two-grade increases in chemistry and haematology laboratory values, with the exception being the proportion of subjects <65 years of age with a two-grade increase in ALT (0% for rezafungin group and 10.6% for the caspofungin group).

Figure 1. Study Drug Discontinuation Prior to Day 14, and SAEs Leading to Death, by Age Group – Safety Population



SAE: Serious adverse event.
Source: Data on File

No data exists for patients below 18 years of age.

- Race

Among the pooled groups, there were race differences overall (i.e., in both treatment groups). White subjects were less likely to have severe/Grade ≥3 TEAEs (43.8% in versus 65.9%, respectively) and SAEs (47.5% versus 60.2%, respectively) than non-White subjects.

TEAEs leading to study discontinuation in the rezafungin group were almost half as frequent in White subjects compared to non-White subjects (13.0% versus 25.6%, respectively), as were SAEs leading to death (17.0% versus 34.9%, respectively); the incidence of these events in the caspofungin group did not show differences between race groups. The incidence of TEAEs was higher in the rezafungin group compared to the caspofungin group for TEAEs (90.0% versus 77.8%, respectively) within the White subject race group.

Taking into account that the incidence was lower for the caspofungin group, it does not seem a center-related problem.

- Sex

Among the pooled groups, the incidence of septic shock in male subjects for both treatment arms was over 3-fold higher than that in female subjects (9.9% versus 3.2%, respectively). The data does not support other differences between males and females.

- Baseline Body Mass Index

Among the pooled groups, the SAE incidence in the rezafungin group compared to the caspofungin group was similar in the <25 kg/m2 (underweight/normal) group (54.5% versus 55.0% subjects, respectively), but was lower for caspofungin in the 25–30 kg/m2 (overweight) group (51.5% versus 40.8% subjects, respectively) and the >30 kg/m2 (obese) group (61.8% versus 38.5% subjects, respectively).

- Baseline Absolute Neutrophil Count

As the Phase 2 STRIVE study excluded subjects with ANC <500/µL, and due to the small sample size of subjects with ANC <500/µL in the ReSTORE study, a meaningful comparison of the data between baseline ANC groups is precluded.

- Baseline Renal Impairment

Among the pooled groups, the proportion of subjects with normal/mild baseline renal impairment with drug-related TEAEs was 18.5% in the rezafungin group compared with 6.7% in the caspofungin group while the proportion was similar in subjects with moderate/severe baseline renal impairment (11.9% versus 15.9%, respectively). The same pattern was observed for SAEs in the normal/mild baseline renal impairment group (50.6% versus 38.9% subjects, respectively) and the moderate/severe baseline renal impairment group (61.0% versus 60.3% subjects, respectively).

Overall, the subjects in the normal/mild baseline renal impairment had higher rates of two grade increases for creatinine than did the moderate/severe baseline renal impairment group (24.9% versus 5.8%).

The applicant precluded the need for adjustment for renal function.

- History of Diabetes Mellitus

Among the pooled groups, the proportion of subjects with at least one cardiac disorder or nervous system disorder TEAE in the rezafungin group was similar for subjects with or without a history of diabetes mellitus (28.8% versus 27.3%, respectively), while there was a difference in caspofungin group for subjects with or without a history of diabetes mellitus (31.9% versus 19.3%, respectively). This difference in the caspofungin group was most apparent in the cardiac disorders SOC for subjects with or without a history of diabetes mellitus (25.5% versus 10.9%, respectively).

- QTc Interval

Study CD101.IV.1.06 was conducted to assess the effects of rezafungin on QT interval corrected for heart rate using Fridericia's formula (QTcF) in healthy adult subjects. Cohorts were treated with single doses of rezafungin 600 mg (n=12), rezafungin 1400 mg (n=12), IV placebo (n=12), or oral moxifloxacin 400 mg plus IV placebo (n=24).

The findings of the study were:

• No effect of rezafungin on the mean QTcF interval.

• No difference in QTcF interval between males and females.

• There were no clinically significant findings in other cardiac parameters, including heart rate (HR), PR interval, and QRS interval between rezafungin (600 mg and 1400 mg) and placebo.

Rezafungin at therapeutic and supratherapeutic doses did not result in clinically meaningful QT prolongation and was well tolerated.

- History of Cardiac Disorder

Among the pooled groups, there were differences overall for history of cardiac disorder (i.e., in both treatment groups). Subjects with a history of cardiac disorders were more likely to have severe/Grade ≥3 TEAEs (61.3% versus 43.4%, respectively) and SAEs (65.5% versus 43.4%, respectively), than subjects without a history of cardiac disease.

The incidence of increased systolic blood pressure (≥180 mmHg and increase of ≥20 mmHg) was 30.2% in the rezafungin group for subjects with a history of cardiac disorder compared to 13.7% for those without a history of cardiac disorder. The same pattern occurred for increased respiratory rate (≥30 breaths/minute and increase of ≥10 breaths/minute) for subjects with a history of cardiac disorder than for those without a history of cardiac disorder (34.6% versus 11.1%, respectively). The incidence of both events in the caspofungin group was not affected by presence or absence of history of cardiac disorder.

There were no noteworthy differences by history of heart failure in AE categories, liver enzyme abnormalities, two-grade increases in chemistry and haematology laboratory values, or vital signs.

Among the pooled groups, there were differences overall for history of arrhythmia (i.e., in both treatment groups). Subjects with a history of arrhythmia were more likely to have severe/Grade ≥3 TEAEs (62.1% versus 45.7%, respectively), SAEs (66.7% versus 46.1%, respectively), and SAEs leading to death (35.6% versus 19.1%, respectively) than subjects without a history of arrhythmia.

The incidence of bradycardia (HR ≤50 bpm and decrease of ≥15 bpm) was higher in the rezafungin group for subjects with a history of arrhythmia than for those without a history of arrhythmia (20.5% versus 1.8%,

respectively), while the rates were similar in the caspofungin group for subjects with or without a history of arrhythmia (14.9% and 13.0%, respectively).

- Baseline Liver Enzyme Elevation

Due to the smaller sample size of subjects with baseline liver enzyme elevation in the rezafungin group (approximately half that of the caspofungin group), a meaningful comparison of the data between baseline liver enzyme elevation groups is precluded.

- Baseline APACHE II Group

Among the pooled groups, there were differences overall for baseline APACHE II score (i.e., in both treatment groups). Subjects with baseline APACHE II score ≥20 were more likely to have SAEs (73.6% versus 48.1%, respectively), and SAEs leading to death (50.9% versus 18.2%, respectively) than subjects with baseline APACHE II score <20.

The incidence of severe/Grade ≥3 TEAEs was lower for subjects with baseline APACHE II score ≥20 in the rezafungin group than in the caspofungin group (57.7% versus 77.8%, respectively), while the rates were similar between treatment groups for subjects with baseline APACHE II score <20 (47.2% and 47.4%, respectively).

There were no other noteworthy differences by baseline APACHE II score in other AE categories, liver enzyme abnormalities, two-grade increases in chemistry and haematology laboratory values, or vital signs.

- Candidemia Only or Invasive Candidiasis

Among the pooled groups, there were differences overall for final diagnosis (i.e., in both treatment groups). Overall, in the pooled data for both subjects who received rezafungin and subjects who received caspofungin, those subjects with final diagnosis of IC were less likely to have TEAEs leading to study discontinuation than subjects with final diagnosis of candidemia only (20.2% for candidemia only versus 10.7% for IC).

The incidence of SAEs leading to death was lower for subjects with final diagnosis of IC in the rezafungin group than in the caspofungin group (9.8% versus 20.9%, respectively), while the rates were similar between treatment groups for subjects with final diagnosis of candidemia only (28.2% and 25.2%, respectively). The same pattern was observed for two grade increases for glucose (i.e., hyperglycaemia), with a lower rate for subjects with final diagnosis of IC in the rezafungin group than in the caspofungin group (2.6% versus 14.6%, respectively), while the rates were similar between treatment groups for subjects with final diagnosis of candidemia only (18.0% and 13.4%, respectively).

The incidence of increased temperature (>38°C and increase of ≥1°C) was lower for subjects with final diagnosis of IC in the rezafungin group than in the caspofungin group (5.1% versus 20.0%, respectively), while the rates were similar between treatment groups for subjects with final diagnosis of candidemia only (24.8% and 18.9%, respectively).

- Hepatic Impairment

Study CD101.IV.1.15 was conducted to assess the impact of moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, using matched healthy adults with normal hepatic function (similar sex, age

within ±10 years of mean age of subjects with chronic liver disease, and body size within 20% of the mean BMI of subjects with moderate or severe hepatic impairment).

The findings of the study were:

• 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, indicating that rezafungin exposure did not change with increasing degree of hepatic impairment.

• Plasma protein binding was similar to controls with normal hepatic function in subjects with moderate hepatic impairment, and was lower in subjects with severe hepatic impairment, which may have been reflective of reduced baseline albumin levels in those subjects.

While moderate and severe hepatic impairment reduced rezafungin exposure, the degree and direction of the exposure change is not considered clinically significant, and the exposure was similar to patients with Candidemia and IC, who also have reduced baseline albumin levels. These findings support no rezafungin dose adjustment in patients with hepatic impairment.

All TEAEs experienced by subjects in the moderate hepatic impairment group were of mild intensity (3/8, 37.5%). All events experienced by subjects in the severe hepatic impairment group were of moderate intensity (3/8, 37.5%, bronchitis, hepatic encephalopathy, hyponatraemia). Only 1 subject with normal hepatic function experienced a TEAE (mild infusion site extravasation).

There were no clinically significant findings in vital signs, ECGs, and physical examination during this study.

- Geographic Region

There were no noteworthy differences between study arms by geographic region.

2.6.8.6. Immunological events

Hypersensitivity to rezafungin and anaphylaxis/anaphylactic shock 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 true immunologically mediated anaphylaxis or anaphylactic shock reactions to rezafungin have not been observed in clinical trials.

The proposed SmPC therefore includes the following in Section 4.3 "Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Hypersensitivity to other medicinal products of the echinocandin class".

2.6.8.7. Safety related to drug-drug interactions and other interactions

Rezafungin does not undergo extensive oxidative metabolism and is not a substrate of drug transporting proteins, so it is unlikely that other drugs will alter rezafungin exposure.

The possible effect of rezafungin on inhibition or induction of drug metabolising enzymes, or inhibition of drug transporters has been ruled out with a combination of in vitro and in vivo studies performed on healthy volunteers in the Phase 1 clinical development programme (Study CD101.IV.1.09 and Study CD101.IV.1.17).

• Study CD101.IV.1.09 conclusions:

Rezafungin had no effects on substrate drugs for CYP2B6 (efavirenz), CYP3A4 (midazolam), CYP1A2 (caffeine) and only minimal increases in repaglinide (CYP2C8), indicating that rezafungin is unlikely to produce clinically relevant drug interactions when co-administered with CYP2B6, CYP3A4, CYP1A2 and CYP2C8 substrates. Rezafungin had no-effect on transporter substrates for OCT-1 and OCT-2 and MATE-1 and MATE-2 (metformin), OATP (pitavastatin) and P-gp (digoxin), and only minimal increases in rosuvastatin (a BCRP and OATP substrate) indicating that rezafungin is unlikely to produce clinically relevant increases in exposure when co-administered with OCT, OATP, MATE, P-gp and BCRP substrates.

Rezafungin produced a small decrease in the average exposure of tacrolimus (a CYP3A4 and P-gp substrate); however, the direction of change indicates that no inhibition of CYP3A4 or P-gp was observed. The small decreases in tracrolimus exposure, which may have been due to an unknown mechanism, are not clinically relevant. These data suggest that no dose adjustments are necessary for tacrolimus when co-administered with rezafungin in a clinical setting.

• Study CD101.IV.1.17 conclusions:

Once weekly IV administration of rezafungin with single doses of cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax did not result in any clinically meaningful change in the exposure of the concomitant medications; the geometric mean ratio of and 90% CI for Cmax and AUC of each drug when administered with rezafungin relative to when the drug was given alone, were largely within the default no-effect boundary of 80–125%. No dose adjustments are necessary for cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax when administered with rezafungin.

No drug interaction studies were performed in the candidemia/IC population.

2.6.8.8. Discontinuation due to adverse events

Phase 1 Studies

There were no TEAEs leading to interruption of study drug in the Phase 1 studies in subjects receiving rezafungin, with the following exception:

• CD101.IV.1.07 (photosensitivity)

o Subject experienced a mild vasovagal reaction at the time the IV was inserted for the Day 22 infusion. The infusion was temporarily paused and resumed after resolution of the event.

Phase 2 Studies

Among the pooled groups, TEAEs leading to interruption of study drug occurred in 2.0% of subjects in the rezafungin group, and 2.4% of subjects in the caspofungin group. No PT occurred in more than 1 subject

across the study treatment groups within the individual studies and pooled data. The most common SOC was infections and infestations with 0.7% and 1.2%, in the rezafungin and caspofungin groups, respectively.

Among the pooled groups, TEAEs leading to interruption of study drug occurred in 2.0% of subjects in the rezafungin group, and 2.4% of subjects in the caspofungin group. No PT occurred in more than one subject across the study treatment groups within the individual studies and pooled data.

Among the pooled groups, TEAEs leading to discontinuation of study drug occurred in 9.3% of subjects in the rezafungin group, and 9.0% of subjects in the caspofungin group. Most PTs did not occur in more than 1 subject across all study treatment groups and pooled data, with the exception of infusion-related reaction in two subjects in the rezafungin group, and chorioretinitis and endophthalmitis in two subjects each in the caspofungin group.

Table 15. Treatment-Emergent Adverse Events Leading to Interruption of Study Drug by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term, n (%)	Phase 2 STRIVE			Phase 3 ReSTORE		Pooled	
	Rezafungin for Injection (Group 1: 400/400 mg) (N = 81)	Rezafungin for Injection (Group 2: 400/200 mg) (N = 53)	Caspofungin (70/50 mg) (N = 68)	Rezafungin for Injection (400/200 mg) (N = 98)	Caspofungin (70/50 mg) (N = 98)	Rezafungin for Injection (400/200 mg) (N = 151)	Caspofungin (70/50 mg) (N = 166)
Number of subjects with at least one TEAE leading to interruption of study drug	0	0	3 (4.4)	3 (3.1)	1 (1.0)	3 (2.0)	4 (2.4)
Infections and infestations	0	0	2 (2.9)	1 (1.0)	0	1 (0.7)	2 (1.2)
Bronchopulmonary aspergillosis	0	0	0	1 (1.0)	0	1 (0.7)	0
Candida sepsis	0	0	1 (1.5)	0	0	0	1 (0.6)
Respiratory tract infection	0	0	1 (1.5)	0	0	0	1 (0.6)
Gastrointestinal disorders	0	0	0	1 (1.0)	0	1 (0.7)	0
Nausea	0	0	0	1 (1.0)	0	1 (0.7)	0
Vomiting	0	0	0	1 (1.0)	0	1 (0.7)	0
Immune system disorders	0	0	0	1 (1.0)	0	1 (0.7)	0
Infusion-related hypersensitivity reaction	0	0	0	1 (1.0)	0	1 (0.7)	0
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (1.0)	0	1 (0.7)	0
Wheezing	0	0	0	1 (1.0)	0	1 (0.7)	0
General disorders and administration site conditions	0	0	0	0	1 (1.0)	0	1 (0.6)
Infusion site extravasation	0	0	0	0	1 (1.0)	0	1 (0.6)
Investigations	0	0	1 (1.5)	0	0	0	1 (0.6)
Liver function test abnormal	0	0	1 (1.5)	0	0	0	1 (0.6)
Renal and urinary disorders	0	0	1 (1.5)	0	0	0	1 (0.6)
Renal impairment	0	0	1 (1.5)	0	0	0	1 (0.6)

MedDRA: Medical Dictionary for Regulatory Activities; N: Number of subjects; n: Number of subjects in the category; PT: Preferred Term; SOC: System Organ Class; TEAE: Treatment-emergent adverse event.
Note: A TEAE is defined as an AE that occurs during or after study drug administration and up through the follow-up visit. A subject with multiple adverse events within an SOC or PT was counted only once. SOCs and PTs within SOC were sorted by descending frequency in the pooled rezafungin for injection column. Percentages were calculated using the total number of subjects in each treatment group (N) as the denominator. MedDRA Version 23.0 was used for reporting adverse events.
Source: ISS Table 2.7.2.

Liver adverse events that resulted in rezafungin discontinuation:

In the ReSTORE study, one of the 98 subjects dosed with rezafungin developed Grade 3 transaminitis with hyperbilirubinemia (considered related, and nonserious) and rezafungin was withdrawn. Post marketing experience

Rezafungin has not been marketed in any region; therefore, no post-marketing data are available. Rezafungin has been available through an expanded access program. One reference is made *Adeel et al. 2021*.

2.6.9. Discussion on clinical safety

Safety database

The most relevant data come from the Phase 2 study STRIVE group 2 and Phase 3 study ReSTORE, as the designs are nearly identical and the rezafungin dosing used was the 400/200 mg one (the same that is intended for approval). Safety data discussed for these studies is presented in the form of pooled data. The applicant counts 151 patients exposed with the 400/200 dose. A total of 409 subjects have been exposed to at least 1 dose of rezafungin. 8 patients were included in the expanded access program.

Duration of exposure and follow-up

For the 400/200 dose regimen (safety population from the Phase 2 STRIVE and Phase 3 ReSTORE studies) the duration of treatment ranged from 1 to 28 days, and median duration of treatment (IV and oral therapy combined) was identical in all study treatment groups and pooled data at 14.0 days.
From the data presented the presence of SAE in subjects receiving rezzafungin was higher in the first week of treatment, declining afterwards, so no dose cumulative SAE is expected and/or anticipated.

Safety profile
No subjects in the Phase 1 studies administered rezafungin experienced TEAEs at an incidence of ≥30%. We can agree with the applicant that only those AE with an incidence above 30%, due to the low number patients included in the Phase 1 studies, are considered, and no SAE were mentioned in the Phase 1 clinical studies.

The most common AE in the Phase 2 (with an incidence above 5%) were by descending frequency hypokalaemia, pyrexia, diarrhoea, anemia, vomiting, nausea, pneumonia, hypomagnesemia, septic shock, abdominal pain, sepsis, constipation and hypophosphatemia. All AE belonging to the SOC Infections and infestations were higher in the rezafungin group with the exception of urinary tract infection.
Of note a class related AE related with the echinocandins class is hyperkalaemia, not found with rezafungin.

There was a total of four potentially related SAEs in the rezafungin group, 1 in the Phase 2 STRIVE Group 1 (400/400 mg) and three in the 400/200 mg dose group across the two studies.

The related SAE in the 400/400 mg group in the Phase 2 STRIVE study was atrial flutter associated with ongoing Day 3 infusions of study drug, which was a saline placebo infusion for those in the rezafungin group; according to the Applicant the atrial flutter associated saline placebo infusion could not be attributable to rezafungin (due to is long ½ life). The other 3 related SAEs in the rezafungin 400/200 mg dose group were first-degree atrioventricular block (asymptomatic), infusion-related reaction, and urticaria (was deemed by the Investigator to be related to oral study drug).

Regarding prolongation of the QTc interval a study was performed (Study CD101.IV.1.06) that did not show a definite relation between rezafungin and prolongation of QTc.

The applicant identified four AESIs: intolerance of the intravenous infusion of study drug, phototoxicity, ataxia, neuropathy and tremor that appear to have been selected on the basis of the safety profiles of other equinocandin antifungal agents and in data from the non-clinical studies.

Intolerance of the intravenous infusion of study drug and phototoxicity are both reflected in the PI.

An independent neurologist's review regarding the causality of tremor concluded that of four cases (in the Phase 2 STRIVE and Phase 3 ReSTORE studies), two were definitely or possibly related to rezafungin treatment. All were mild in intensity, and were easily treated by correction of serum electrolytes, or resolved without treatment. Considering the preclinical signal of tremors as well as phospholipidosis in sensory ganglia and peripheral nerves and given that there are 5 events of tremor, reported in rezafungin treated patients v none in caspofungin, further monitoring for this as a potential AE is required. Given the confounders, it is difficult to conclude if rezafungin may have played a role with tremor in these cases. It is also the case that the safety database is limited, and the numbers exposed may not yet be sufficient to fully evaluate this risk.

There were no subject deaths in any of the Phase 1 studies. The incidence pattern of SAEs resulting in death was similar across the study treatment groups and pooled data. The most common SOC was Infections and infestations (9.3% and 14.5% subjects in the rezafungin and caspofungin groups, respectively).

No trend was found in the rezafungin group that could be related to the death cases.

A total of 12/149 of the rezafungin pool had ALT > 3 X ULN, i.e. including those with higher grade rises (> 5ULN, >8ULN,>10ULN) and a total 18/49 of the rezafungin pool had AST > 3 X ULN, i.e. including with higher grade rises. These numbers are higher than those found with caspofungin.

It must be noted that most patients that met Hy's law had indeed confounding factors: major trauma, sickle cell anaemia, penetrating liver injury and three had bacterial septic shock that resulted in death. The occurrence of a drug liver injury was unlikely but could not be ruled out; further clarification was provided in the 7 cases of Hy's lawand also in the 2 cases of DILI.

Considering that the data provided could not rule out a serious risk of hepatotoxicity for rezafungin the applicant has agreed that a warning on hepatic effects was added to section 4.4, in line with the existing information in the other authorised products of the echinocandin class.

Apparently, there was a trend to lower AEs in subjects >65years and BMI >30 Kg/m^2; no significative differences were found regarding race and sex and geographic region.

To date, no patients below 18 years of age were included in the clinical studies and the indication is restricted to adult patients, although a PIP is in place.

It is of note that the Phase 2 STRIVE study excluded subjects with ANC <500/µL, but form the data presented (although a very small number o patients had a ANC <500/µL, no safety issues were anticipated.

As expected, an increase in SAEs was higher in patients with higher APACHEII scores and an history of cardiac disorder, although the number of patients in each of these groups was small to make any conclusion.

Patients with IC had more TEAEs than patients only with candidemia, as expected.
There is a recognised risk of hypersensitivity associated with use of equinocandins. Hypersensitivity to rezafungin and anaphylaxis/anaphylactic shock Mild- moderate allergic reactions were reported uncommonly, occurring in 0.1-1% of subjects administered rezafungin. This information is reflected in the SmPC.

Among the pooled groups, TEAEs leading to interruption of study drug occurred in 2.0% of subjects in the rezafungin group, and 2.4% of subjects in the caspofungin group. No PT occurred in more than one subject across the study treatment groups within the individual studies and pooled data.

ADRs in the SmPC

Section 4.8 is as follows:

System organ class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Not Known
Blood and lymphatic system disorders		Anaemia		
Metabolism and nutrition disorders	Hypokalaemia	Hypomagnesaemia, hypophosphataemia	Hyperphosphataemia, hyponatraemia	
Vascular disorders		Hypotension		
Respiratory, thoracic and mediastinal		Wheezing		
Gastrointestinal disorders	Diarrhoea	Vomiting, nausea, abdominal pain, constipation		
Skin and subcutaneous tissue disorders			Phototoxicity	Urticaria
Musculoskeletal and connective tissue disorders			Tremor	
General disorders and administration site conditions	Pyrexia			
Investigations		Blood alkaline phosphatase increased, hepatic enzymes increased, alanine aminotransferase increased, aspartate aminotransferase	Eosinophil count increased	

		increased, blood bilirubin increased		
Injury, poisoning and procedural complications		Infusion-related reactions		

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Description of selected adverse reactions

Infusion reactions resolved within minutes, some without interruption or discontinuation of infusion. For those that required stoppage of the infusion, infusion could be restarted at a lower rate once symptoms had resolved (see section 4.2 and 4.4).

According with the applicant transient infusion-related reactions were characterized by flushing, sensation of warmth, nausea, and chest tightness, tha applicant should discuss why only infusion realated reactions was added and not weezing and erythema; the same is true for rash, related to hypersensitivy reactions.

Assessment of paediatric data on clinical safety

No patient below 18 years of age was included in the clinical trials. A PIP is programmed to end by 2025.

2.6.10. Conclusions on the clinical safety

There were objections based on the observed clinical safety profile:
The fact that there were 7 patients meeting Hy's criteria after starting rezafungin, as well as at least separate 2 DILI AEs reported in rezafungin arms, versus none in the caspofungin arm, was of significant concern.

It has to be noted that most patients that met Hy's law had indeed confounding factors: major trauma, sickle cell anaemia, penetrating liver injury and three had bacterial septic shock that resulted in death. The occurrence of a drug liver injury was unlikely, but could not be ruled out; further clarification was provided in the 7 cases of Hy's law and also in the 2 cases of DILI.

Taking into account that the data provided could not rule out a serious risk of hepatotoxicity for rezafungin the applicant has agreed that a warning on hepatic effects was added to section 4.4, in line with the existing information for other authorised products of the echinocandin class.

2.7. Risk Management Plan

2.7.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

2.7.1.1. Discussion on safety specification

The Committee considers the data presented in the RMP as follows:

- **Epidemiology of the indications and target population**

This has been adequately described, noting that patients <18 years of age were not included.

- **Clinical trial exposure**

The RMP reports that 409 subjects were exposed to any dose of rezafungin in the clinical studies with an duration of exposure that ranged from 1-28 days; 154 were males and 155 were females.
219 patients were included with a CrCL<60 mL/min, 40 with hepatic impairment (Child-Puig not specified) and 91 with cardiac impairment (not specified).

- **Populations not studied in clinical trials**

-Patients <18 years old

-Pregnant or lactating women

-Patients with a child-Puig score>9

-ALT and/or AST>10 fold the upper normal limit

- Patients with 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). Planned or ongoing therapy at Screening with a known neurotoxic medication; and that meet CTCAE criteria for ataxia, tremor, motor neuropathy, or sensory neuropathy of Grade 2 or higher.

- **Post-authorisation experience**

No post-authorisation data is available.

- **Additional EU requirements for the safety specification**

Potential for misuse for illegal purposes

Not applicable.

2.7.1.2. Conclusions on the safety specification

The list of safety concerns is in accordance with the recommendation given in the GVP Module V rev. 2.

2.7.2. Pharmacovigilance plan

In the List of the Outstanding Issues D180, the Applicant was requested to discuss how missing information: Use in pregnancy and lactation will be further characterised, and appropriate post-authorisation measure should be proposed.

The Applicant provided RMP ver.1.0 dated 06.09.2023. The Applicant has proposed routine pharmacovigilance activities to monitor the above-mentioned missing information, which is acknowledged. The rationales are:

- ✓ Due to the limited number of pregnant or breastfeeding patients with invasive candidiasis or candidemia, and the low likelihood that these patients would be treated with rezafungin, the Applicant expects enrolment of appropriate patients into studies or registries to further characterise use in pregnancy and lactation would be negligible, thus making such studies non-feasible.
- ✓ Non-clinical studies did not identify any developmental toxicity or safety signals related to use in pregnancy or lactation.
- ✓ Routine pharmacovigilance activity as described in Applicant's relevant SOP as part of pharmacovigilance Quality Management System (QMS) includes the reporting of pregnancy exposures with and without associated adverse events, and a robust targeted follow-up questionnaire at the time of reporting the exposure as well as follow-up around the expected delivery date. The same QMS also includes process for capturing reports of use during lactation.
- ✓ Employing routine pharmacovigilance activities for monitoring this topic would be proportionate for the safety profile of rezafungin, is consistent with RMPs of products in this therapeutic class, and is in line with GVP module V and the draft for GVP Product or Population-Specific Considerations III: Pregnant and breastfeeding women.

Despite the fact that the Applicant has updated Part III, Part III.1 Routine Pharmacovigilance Activities needed some revision (see below):

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

The Applicant provided an updated RMP as requested, in which all issues were addressed satisfactorily and resolved.

2.7.3. Risk minimisation measures

Table 16. 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.

The Applicant has revised Part V.

2.7.4. Summary of the risk management plan

The public summary of the RMP does not require revision.

2.7.5. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 dated 29.09.2023 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 22.03.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Rezzayo (rezafungin) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic context

3.1.1. Disease or condition

Invasive candidiasis is an infection caused by yeast called *Candida* when it has spread widely in the body and may also be present in blood. The infection generally occurs in patients whose immune system has been weakened or when damage in body tissues allows the infection to spread.

Invasive candidiasis can cause fever and chills which do not improve with antibiotics. The infection may cause the patient to go into shock with low blood pressure, racing heartbeat and rapid breathing. Spread of the infection can damage organs such as kidneys, heart, liver, spleen, lungs, eyes and brain.

This is a life-threatening disease that can be fatal due to damage to vital organs.

Any delay in initiation of appropriate antifungal therapy results in increased morbidity and mortality.

3.1.2. Available therapies and unmet medical need

Most clinicians choose an echinocandin (anidulafungin, caspofungin or micafungin) as first-line therapy for adult patients with IC. Echinocandins are effective, safe and have very limited drug–drug interactions; however, they require intravenous administration. A limitation for their use is the need for daily IV administration due to their short half-life.

The current ESCMID guidelines state that oral step-down therapy with fluconazole can be used to simplify treatment if the patient is stable, tolerates the oral route and if the species is susceptible. Other agents used to treat Candida infections include the azoles (fluconazole, itraconazole) and polyenes (amphotericin B products). However, Amphotericin B products are now largely confined to second or later line use in patients failing or refractory to echinocandins or azoles, except in chronic disseminated (hepatosplenic) candidiasis.

Rezafungin is a next-generation echinocandin derived from anidulafungin, designed to achieve improved chemical and metabolic stability and PK (longer half-life consistent with once weekly dosing). These adaptations, in turn, yielded multiple properties that differentiate rezafungin and potentially give patients and clinicians additional options beyond those of currently marketed antifungal agents.

3.1.3. Main clinical studies

The main evidence of efficacy submitted comes from 'ReSTORE': a Phase 3, Multicenter, Randomized, 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 Invasive Candidiasis.

3.2. Favourable effects

Based on the Applicant's primary analysis, which employed a 20% NI margin, the Phase 3 ReSTORE study demonstrated that rezafungin could be as effective as caspofungin in the treatment of invasive candidiasis. A difference in the global response at day 14 (comprised by clinical cure, radiological cure and mycological eradication) of -1.1 was observed for rezafungin compared to caspofungin (95% C.I.: -14.9, 12.7). Secondary analysis and sensitivity analysis were supportive of the results.

3.3. Uncertainties and limitations about favourable effects

Some forms of invasive candidiasis were not studied and the results of the studies cannot be extrapolated to these conditions.

A study comparing patients with and without elimination of the suspected focus of infection, namely intravascular catheters and/or and effective drainage of collections of infected material (a clinical intervention essential to the successful management of IC) was not carried out.

The chosen 20% NI margin is considered to be too wide to adequately assess the efficacy of rezafungin when compared to caspofungin. Even with a NIM of 15%, the outcome with a lower bound of the 95% CI of the difference in Global response compared with caspofungin (slightly above -15%) and the upper bound of the 95% CI of the difference in ACM (slightly below 15%), raises concerns of a potential unacceptable loss of antifungal effect, which might not be compatible with clinical utility.

When asked to further justify that the clinical efficacy data supports a positive benefit-risk balance for the intended indication the applicant explained that, given the difficulty in the recruitment of patients, the non-inferiority margin of 20% was chosen to allow for a reasonable number of subjects included in a smaller period of time.

The concerns raised by the pre-defined primary analysis results were not entirely resolved by the applicant's multiple alternative analyses presented, including several *post hoc* analyses. The applicant was not able to establish that rezafungin has important advantages in terms of spectrum, efficacy or safety over the approved agents in the same class for treatment of candidiasis. At the same time, there are relatively few antifungal agents available, and the overall assessment of the efficacy findings, including the results for the pre-defined primary endpoint of ACM at day 30 (although not the EU-preferred primary endpoint), supports a conclusion that rezafungin has efficacy in the population studied.

Considering the small numbers of neutropenic patients (7,5% of patients in the Phase 3 study) and of patients with APACHE II scores ≥ 20, the Applicant recognised that the number of neutropenic subjects included in the dataset is small, but it is as expected and is in line with other IC studies in neutropenic subjects. These subjects often have prophylactic antifungal treatment and are difficult to recruit into clinical studies of IC. However, there is nothing to suggest that rezafungin performs differently in neutropenic vs non-neutropenic subjects, or when compared with caspofungin in neutropenic subjects in terms of benefits and risks. Regarding Safety, no serious treatment-related adverse events were observed with rezafungin in neutropenic subjects in the development programme. However, as cautious approach and to reflect the small numbers of subjects with an ANC <500, the following updates have been made to the SmPC (clean and track changes):

Section 4.4: "*Efficacy of rezafungin was only evaluated in a small number of neutropenic subjects (see Section 5.1)"*.

Section 5.1: *"For rezafungin and caspofungin treatment groups, 88.0% and 93.9% subjects, respectively, had an ANC ≥ 500/mm^3 at baseline."*

Neutropenic subjects have a compromised immune system and are therefore at particular risk from infections. These subjects are particularly in need of effective anti-infective treatments. Echinocandins have been shown to have a positive benefit-risk assessment in neutropenic subjects and rezafungin treatment data do not suggest it should perform differently in these subjects. Therefore, although the data in neutropenic patients were limited for Rezzayo, similar effects in non-neutropenic and neutropenic patients at the same dose level as other already approved echinocandins could be anticipated also for Rezzayo. Considering that there was a limited number of neutropenic subjects included for analysis but also that the submitted data does not suggest a diminished efficacy of rezafungin in patients with neutropenia (as with other echinocandins), the inclusion of this population in the proposed indication is acceptable. The information regarding this issue proposed to be included in sections 4.4 and 5.1 of the SmPC is also acceptable.

A small number of resistant isolates was found, so a "more" favourable effect regarding potential resistance over caspofungin cannot be ascertained.

3.4. Unfavourable effects

With the data provided, a serious risk of hepatotoxicity cannot be ruled out, as for other echinocandins.

3.5. Uncertainties and limitations about unfavourable effects

With the data provided, a serious risk of hepatotoxicity cannot be ruled out. There were 7 patients meeting Hy's criteria after starting rezafungin, as well as at least separate 2 DILI AEs reported in rezafungin arms, versus none in the caspofungin arm.

It has to be noted that most patients that met Hy's law had confounding factors: major trauma, sickle cell anaemia, penetrating liver injury and three had bacterial septic shock that resulted in death. The occurrence of a drug liver injury was unlikely but could not be ruled out; further clarification was provided in the 7 cases of Hy's law and also in the 2 cases of DILI.

Taking the above into account, the applicant agreed to the recommendation that a warning on hepatic effects be added to section 4.4, in line with the existing information in the other authorised products of the echinocandin class.

3.6. Effects table

Table 17. Effects table for rezafungin in the treatment of invasive candidiasis (data cut-off: 31 Nov 2021).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Global response at D14	Clinical cure, radiological cure and mycological eradication	Number (percentage)	Rezafungin 400/200 mg weekly: 55 (59.1%)	Caspofungin 70 mg/ 50 mg Daily: 57 (60.6%)	-20% NI margin (treatment difference -1.1, 95% confidence interval -14.9, 12.7) -not comparing between patients with and without catheters -small number of neutropenic patients included and with APACHE>20 -small number of resistant isolates	(1)
Unfavourable Effects						
Hepatotoxicity	Cases of Hy's law and DILI	/	Rezafungin 400/200 mg Weekly, Rezafungin 400/400 mg, weekly	Caspofungin 70 mg/ 50 mg Daily	Hepatotoxicity cannot be ruled out for rezafungin.	(1)(2)(3)

Notes:
(1)ReSTORE Clinical Phase III Study
(2)STRIVE Clinical Phase II Study
(3)pooled data from group II STRIVE and ReSTORE Clinical Study

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Rezafungin powder for concentrate for solution for infusion (rezafungin) is a new echinocandin for the treatment of invasive candidiasis (IC). It is structurally similar to currently approved echinocandins, a class of antifungals with an established mode of action and safety profile, that is generally aligned with the available knowledge for this class of antifungals. Rezafungin selectively inhibits 1,3-β-D-glucan synthase, an enzyme present in fungal, but not mammalian, cells. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall. The synthesis of 1,3-β-D-glucan is dependent upon the activity of synthase complex, in which the catalytic subunit is encoded by FKS1, FKS2, and FKS3 genes. Inhibition of 1,3-β-D-glucan synthesis results in rapid and concentration-dependent fungicidal activity in *Candida* species

(spp.). Rezafungin's spectrum of activity covers numerous fungal spp., including *Candida* spp., *Aspergillus* spp., *Pneumocystis* spp. and dermatophytes. Poor activity is observed for rezafungin against *Cryptococcus neoformans* and rare moulds (i.e., Mucorales, *Fusarium* spp., *Scedosporium* spp.), similar to that of other echinocandins.

The completed clinical development programme to support this submission consisted of eight Phase 1 safety, pharmacokinetic (PK)/ pharmacodynamic (PD) and other clinical pharmacology studies in healthy subjects or special populations, together with a Phase 2 (STRIVE) and pivotal Phase 3 (ReSTORE) studies that evaluated the clinical safety and efficacy of rezafungin in the treatment of IC, including candidemia.

Based on the applicant's primary analysis, which employed a 20% NI margin, the Phase 3 study demonstrated that rezafungin could be as effective as caspofungin in the treatment of invasive candidiasis. A difference in the global response at day 14 (comprised by clinical cure, radiological cure and mycological eradication) of -1.1 was observed for rezafungin compared to caspofungin (95% C.I.: 14.9, 12.7). Secondary analysis and sensitivity analysis were supportive of the results.

The concerns raised by the pre-defined primary analysis results were not entirely resolved by the applicant's multiple alternative analyses presented, including several *post hoc* analyses. The opinion on the indication is based on the following results:

	REZZAYO 400 mg/200 mg N = 93 n (%)	**Caspofungin 70 mg/50 mg N = 94 n (%)**	**Difference (95% CI) [a]**
All-Cause Mortality (Day 30) [b]	22 (23.7)	20 (21.3)	2.4 (-9.7, 14.4)
Global Cure [c]			
Day 5	52 (55.9)	49 (52.1)	3.8 (-10.5, 17.9)
Day 14	55 (59.1)	57 (60.6)	-1.5 (-15.4, 12.5)
Clinical Cure [d]			
Day 5	59 (63.4)	70 (74.5)	-11.0 (-24.0, 2.3)
Day 14	62 (66.7)	63 (67.0)	-0.4 (-13.8, 13.1)
Day 30	51 (54.8)	52 (55.3)	-0.5 (-14.6, 13.7)
Mycological eradication/presumed eradication [e]			
Day 5	64 (68.8)	58 (61.7)	7.1 (-6.6, 20.6)
Day 14	63 (67.7)	62 (66.0)	1.8 (-11.7, 15.2)

[a] Two-sided 95% confidence intervals (CIs) for the observed differences in cure rates (REZZAYO minus caspofungin) is calculated using the unadjusted methodology of Miettinen and Nurminen.
[b] Patients who died on or before Day 30, or with unknown survival status.
[c] Patients with a mycological eradication/presumed eradication, clinical cure and radiologic cure (for patients with IC documented by radiologic or other imaging findings at baseline), as adjudicated by the Data Review Committee.
[d] Investigator's assessment of clinical response based on resolution of attributable systemic signs and symptoms of candidemia/IC, no new systemic signs or symptoms attributable to candidemia/IC, no new systemic antifungal therapy to treat candidemia/IC, and the subject is alive.
[e] Negative blood culture or culture from a normally sterile site and no change in antifungal therapy for the treatment of candidemia and/or IC. For IC patients, if the normally sterile baseline site of *Candida* infection was not accessible, the patient was presumed to have an eradication if the clinical outcome and radiologic outcome (if assessed) was a cure.

This study was designed and powered to address both the FDA-preferred (ACM) and the EU-preferred (global response) primary endpoints. For the EU-recommended primary endpoint, the previously reported Day 14 analysis of global cure gives a lower bound of the CI that is just below 15%. The lower bound of the 95% CI was within -10% for the FDA-recommended primary endpoint of ACM at day 30 in the mITT population.

For clinical cure, the analyses at each timepoint suggest that rezafungin is not as effective as caspofungin. However, the day 5 results for global cure and the day 5 and 14 results for mycological eradication are generally supportive of comparable efficacy.

It is also recognized that the secondary and exploratory endpoints from the ReSTORE study, as well as sensitivity analysis, support the results obtained for the primary endpoint. However, the greater than 10% NIM chosen provides some uncertainty in the compared efficacy of rezafungin with caspofungin (or other echinocandins).

The applicant was not able to establish that rezafungin has important advantages in terms of spectrum, efficacy or safety over the approved agents in the same class for treatment of candidiasis. At the same time, there are relatively few antifungal agents available, and the overall assessment of the efficacy findings, including the results for the pre-defined primary endpoint of ACM at day 30 (although not the EU-preferred primary endpoint), supports a conclusion that rezafungin shows efficacy in the population studied.

For the reasons presented above, despite the fact that the requirements as laid down in CHMP guidance have not strictly been met, but noting that there is no prescribed non-inferiority margin stated in that guidance, consideration was given to its approval. There is some uncertainty in the compared efficacy of rezafungin with caspofungin which is likely to be a result of the relatively small size of the pivotal study. However, this uncertainty was not considered to outweigh the approvability of Rezzayo based on the available data. Efficacy was considered established and an indication with section 5.1 reflecting the limitations was acceptable.

Regarding the small numbers of neutropenic patients (7,5% of patients in the Phase 3 study) and of patients with APACHE II scores ≥ 20, the available data for other echinocandins showed that efficacy can be anticipated in neutropenic patients at the same dose level as in non-neutropenic patients. Therefore, although the data in neutropenic patients treated with Rezzayo are limited, similar effects in non-neutropenic and neutropenic patients at the same dose level could be anticipated also for Rezzayo. This was considered to be additionally supportive of a non-restricted indication.

Some unfavourable effects seem more frequent with rezafungin than with caspofungin, namely the presence of a potential hepatotoxicity risk. In terms of clinical safety, the fact that there were 7 patients meeting Hy's criteria after starting rezafungin, as well as at least separate 2 DILI AEs reported in rezafungin arms, versus none in the caspofungin arm, was of concern. Most patients that met Hy's law had confounding factors: major trauma, sickle cell anaemia, penetrating liver injury and three had bacterial septic shock that resulted in death. The occurrence of a drug liver injury was unlikely but could not be ruled out; further clarification was provided in the 7 cases of Hy's law and also in the 2 cases of DILI.

Therefore, a warning on hepatic effects is in section 4.4 of the SmPC, in line with the existing information in the other authorised products of the echinocandin class.

3.7.2. Balance of benefits and risks

The overall benefit /risk balance of rezafungin is considered to be positive.

3.8. Conclusions

The overall benefit/risk balance of Rezzayo is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Rezzayo is favourable in the following indication:

treatment of invasive candidiasis in adults

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that rezafungin is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

5. Appendix

5.1. CHMP AR on New Active Substance (NAS) dated 12 October 2023