NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Rezafungin for previously untreated invasive candidiasis

Company/Developer	Napp Pharmaceuticals Ltd.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 23920	NICE ID: 10768	UKPS ID: 664579

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Rezafungin is in development for the treatment of adult patients with previously untreated invasive candidiasis. Invasive candidiasis is a severe form of a common fungal infection that would normally affect the skin, but in the invasive form, infects the patients' blood (candidaemia) or organs (e.g., brain, lungs, and the circulatory system). This is most common in patients who have other serious medical conditions which means their immune system can't fight off the infection before it spreads around the body. Hospitalised patients, particularly those in intensive care are especially susceptible to invasive candidiasis infection.

Rezafugin works by stopping the outside barrier of the fungal cells from forming correctly, making them unstable and causing them to die. Rezafungin is administered intravenously once weekly, whereas current recommended treatments are required to be administered daily. If licensed, rezafungin would offer a new alternative treatment to adult patients newly diagnosed with invasive candidiasis.

Proposed Indication

Treatment of candidemia and/or invasive candidiasis in adult patients.[1]

Technology

Description

Rezafungin (Rezzayo, CD101) is a novel, once-weekly antifungal medication being developed for the treatment and prevention of serious fungal infections including invasive candidiasis and candidemia.[2] Rezafungin is a new β-glucan synthase inhibitor that is chemically related with anidulafungin, and is considered the first molecule of the new generation of long-acting echinocandins. In Candida fungal species, the fungal cell wall is formed by mannosylated proteins fixed to the carbohydrate core by glycosylphosphatidylinositol residues, and rezafungin inhibits these forming the cell wall resulting in osmotic instability and cell death.[3,4]

In the phase III trial (NCT03667690), rezafungin was given via intravenous (IV) infusion (400mg loading dose in week one followed by 200mg once weekly for a total of two to four weeks) to adult patients with candidemia and/or invasive candidiasis who were previously untreated.[1]

Key Innovation

Echinocandins that are currently in use have several pharmacological problems including poor oral absorption, short half-lives which make daily IV dosing necessary, and chemical instability resulting in problems storing and manufacturing the products. Rezafungin has been developed to circumvent many of these issues- it is more stable and is only required to be administered once-weekly making it a treatment option for both hospitalised patients and out-patients.[3,5] High front loaded dosing of rezafugin results in rapid Candida clearance and it has been found to be active against hard to treat strains such as Candida auris and azole-resistant Candida.[6]

If licensed, rezafungin will offer a new first-in-line treatment option for adult patients diagnosed with invasive candidiasis or candidemia.

Regulatory & Development Status

Rezafugin does not currently have Marketing Authorisation in the EU/UK for any indication.

Rezafugin is also in phase III/II clinical development for:[7]

- Pneumocystis
- Aspergillus
- Mycoses
- Yeast infections
- Vulvovaginal moniliasis
- Monilial vaginitis

Rezafugin has the following regulatory designations/awards:

- A PIM status for the treatment of treatment of invasive candidiasis by the MHRA in March 2022[8]
- An orphan drug designation in the EU in 2021 for the treatment of invasive candidiasis[9]
- Fast track status by the FDA for the treatment of candidemia and invasive candidiasis in May 2015[10]

Patient Group

Disease Area and Clinical Need

Invasive candidiasis is an infection caused by a yeast called Candida, which has spread widely in the body and may also be present in blood. A Candida bloodstream infection, also called candidemia, is the most common form of invasive candidiasis.[11] 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, therefore it can be a life-threatening disease that can be fatal.[9] Systemic/invasive candidiasis can lead to sepsis and/or organ specific infections such as pneumonia, meningitis, endocarditis, and mucocutaneous, osteoarticular, hepatosplenic, and peritoneal infections.[12] People who are at the highest risk for developing invasive candidiasis include those who; have spent significant amounts of time as a patient in intensive care units; have central venous catheters, are immunocompromised, have had recent surgery or large amounts of antibiotics, have kidney failure, or babies born prematurely.[13]

The reported incidence rate of candidaemia in England (2017) was 3.5 patients per 100,000, with highest rates seen in males, and those patients over the age of 75 years.[14] A high proportion of patients in intensive care units (ICU) develop candidaemia (5-10 patients per 1,000 admissions), but only 5-30% of them develop into invasive candidiasis.[15] In England (July 2009- March 2011), 359 patients were admitted to the ICU with invasive candidiasis.[16] Systemic/invasive candidiasis has an estimated mortality rate of up to 79%.[12] In England (2020-21), there were 377 finished consultant episodes (FCE) for candida sepsis (ICD-10 code: B37.7) with 146 hospital admissions that resulted in 3,173 FCE bed days and 21 day cases.[17]

Recommended Treatment Options

For invasive candidiasis, treatment with an echinocandin is recommended. Fluconazole is an alternative for Candida albicans infection in clinically stable patients who have not received an azole antifungal recently. Amphotericin B is an alternative when an echinocandin or fluconazole cannot be used, however, amphotericin B should be considered for the initial treatment of CNS candidiasis. Voriconazole can be used for infections caused by fluconazole-resistant Candida spp. when oral therapy is required, or in patients' intolerant of amphotericin B or an echinocandin. In refractory cases, flucytosine can be used with intravenous amphotericin B.[18]

Clinical Trial Information

Trial	**ReSTORE; NCT03667690;** A Phase 3, Multicenter, Randomized, Double-blind Study of Rezafungin Compared to Caspofungin in Subjects With Candidemia and/or Invasive Candidiasis **Phase III** - Complete **Location(s):** Six EU countries, USA, Australia, China and other countries **Study completion date:** October 2021	**STRIVE; NCT02734862;** A Phase 2, Multicenter, Randomized, Double-blind Study of the Safety, Tolerability, and Efficacy of Intravenous CD101 Compared to Caspofungin Followed by Oral Step Down in Subjects With Candidemia and/or Invasive Candidiasis-Bridging Extension **Phase II** - Complete **Location(s):** Five EU countries, USA, Canada and other countries

		Study completion date: July 2019
Trial Design	Randomised, parallel assignment, double-blinded	Randomised, parallel assignment, double-blinded
Population	N= 199; Subjects who have tested positive for Candida Species pluralis (spp.) and have the presence of one or more systemic signs attributable to candidemia or invasive candidiasis appearing; aged 18 years and older	N= 207; Subjects who have tested positive for Candida Species pluralis (spp.) and have the presence of one or more systemic signs attributable to candidemia or invasive candidiasis appearing; aged 18 years and older
Intervention(s)	Rezafungin intravenous (IV), 400mg loading dose followed by 200mg once weekly for a total of two to four doses	Rezafungin (IV), 400mg loading dose followed by 200mg once weekly for a total of two to four doses
Comparator(s)	Caspofungin (IV), 70mg loading dose followed by 50mg daily for up to 28 days. After ≥3 days of caspofungin treatment subjects may be switched to oral step-down therapy of fluconazole (6 mg/kg to the nearest 200 mg).	Caspofungin (IV), 70mg loading dose followed by 50mg daily for up to 28 days. After ≥3 days of IV therapy, subjects in the caspofungin group can be switched to oral step-down therapy of fluconazole (a loading dose of 800 mg [4 capsules] on the first day followed by 400 mg [2 capsules]/day thereafter).
Outcome(s)	Primary outcome measures: • All-cause mortality [time frame: day 30 (-2 days)] • Global cure [time frame: day 14 (±1 day)] See trial record for full list of other outcomes	Primary outcome measures: • Incidence of treatment emergent adverse events [time frame: from first dose up to 59 days] • Resolution of systemic signs attributable to candidemia and/ or invasive candidiasis and mycological eradication [time frame: day 14 (± 1 day)] See trial record for full list of other outcomes
Results (efficacy)	Both all-cause mortality at day 30 as well as global cure at day 14 were achieved. Early efficacy outcomes (day 5 global cure, day 5 mycological eradication) were either similar or trended higher in the rezafungin arm. Blood cultures were cleared more quickly in the rezafungin arm though the difference was not significant. Duration of intensive care unit stay was lower in the rezafungin group compared to caspofungin.[6]	Of 207 patients enrolled, overall cure rates for rezafungin were 60.5%-76.1% depending on dose given, and 67.2% for the active comparator caspofungin. Candidemia was cleared in 19.5 and 22.8 hours in rezafungin and caspofungin patients, respectively.[19]

Results (safety)	Rates of adverse events and serious adverse events were similar between the two study arms.[6]	Safety and tolerability findings were comparable between treatments, consistent with the established safety profile of the echinocandin class. Additional safety endpoints, including liver function tests, were evaluated in patients with candidemia and/or invasive candidiasis treated with rezafungin once-weekly compared with caspofungin once daily. Data demonstrate comparable safety of rezafungin to caspofungin in patients with candidemia and/or invasive candidiasis.[20]

Estimated Cost

The cost of rezafungin was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE quality standard. Antimicrobial stewardship (QS121). April 2016.
- NICE guideline. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NG15). August 2015.
- NICE diagnostic guidance. SepsiTest assay for rapidly identifying bloodstream bacteria and fungi (DG20). February 2016.
- NICE Medtech innovation briefing. Fungitell for antifungal treatment stratification (MIB118). August 2017.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- Leeds Teaching Hospitals NHS Trust. Guidelines for the treatment of candidaemia and invasive candidiasis in adult patients. 2019.[21]
- Whittington Health NHS. Antifungal guideline for invasive fungal infections in adults. 2019.[22]
- European Society of Clinical Microbiology and Infectious Diseases (ESCMID). ESCMID guideline for the diagnosis and management of candida diseases 2012: non-neutropenic adult patients. 2012.[23]
- Arden Cancer Network NHS. Guidelines for the management of invasive fungal infections in adult haematology and oncology patients. 2010.[24]

Additional Information

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