A Phase 3, Multicenter, Randomized, Double-Blind Study of the Efficacy and Safety of Rezafungin for Injection Versus the Standard Antimicrobial Regimen to Prevent Invasive Fungal Diseases in Adults Undergoing Allogeneic Blood and Marrow Transplantation (The ReSPECT Study)

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The primary objectives are:* United States Food and Drug Administration (FDA) primary objectiveTo demonstrate noninferiority in subjects who received an allogeneic BMT for subjects randomized to Rezafungin for Injection compared to subjects...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Fungal infectious disorders
Study type	Interventional

Summary

ID

NL-OMON49120

Source
ToetsingOnline

Brief title
ReSPECT

Condition

- Fungal infectious disorders

Synonym
Invasive Fungal Diseases / Fungal Disease

Research involving
Human

Sponsors and support

Primary sponsor: Cidara Therapeutics Inc.
Source(s) of monetary or material Support: Cidara Therapeutics Inc.

Intervention

Keyword: Blood and marrow transplant (BMT), Phase 3, Rezafungin

Outcome measures

Primary outcome

Efficacy

To evaluate the FDA and EMA primary objective, the primary efficacy endpoint is fungal-free survival at Day 90 (±7 days), as defined by:

* Survival, and

* Absence of proven or probable IFD. Proven and probable IFD are defined per the modified European Organization for Research and Treatment of Cancer Mycoses Study Group (EORTC-MSG) criteria as follows (see Appendix 4 for complete IFD definitions):

o Proven Candida infection documented by clinical criteria plus positive culture or gram stain from a normally sterile site; probable Candida infection documented by clinical criteria plus a positive *-D glucan assay.

o Proven mold infection documented by clinical criteria plus culture from a normally sterile site and/or histopathologic evidence of mold; probable mold infection documented by clinical criteria plus GM antigen positivity and/or

positive culture from non-sterile site, or positive *-D glucan assay

o Proven PCP documented by clinical criteria plus histopathology plus microbial evidence of disease by antigen from BAL fluid; Probable PCP documented by clinical criteria plus microbial evidence provided by antigen from sputum, or two positive *-D glucan assays

* Absence of: receipt of non-study drug systemic antifungal therapy (including anti-PCP drugs) for a cumulative exposure >10 days. Other anti-PCP drugs include dapsone, atovaquone, pentamidine (IV or inhaled), and combined clindamycin and primaquine.

For the EMA primary objective, subjects treated with a cumulative duration of standard of care antifungal therapy exceeding 10 days during the 90-day period of study drug administration will be considered a prophylaxis failure. Discontinuations of study drug due to issues of toxicity or tolerability will not be incorporated into the primary outcome assessment.

Secondary outcome

To evaluate secondary efficacy objectives, secondary efficacy endpoints include:

* Study drug withdrawal due to toxicities or intolerance

* Cumulative incidence of proven and probable IFD including numbers of invasive infection from

Candida spp., Aspergillus spp., and Pneumocystis jirovecii

* Time to IFD or death, defined as the number days from the first dose of study drug to the date of proven or probable IFD or death (all-cause). Subjects who do not have an event will be censored at the date last

known to be IFD-free or alive. Subjects who are lost to follow-up will be

censored at the date of last contact.

* All-cause mortality

* Attributable mortality associated with IFD

Efficacy assessments will be made on Day 14 (±1 day), Day 28 (±1 day), Day 60

(±5 days), Day 90 (±7 days), and Day 120 (±7 days).

Study description

Background summary

A common side effect of a bone marrow transplant (BMT) is a decrease in the number or strength of white blood cells, whose function is to fight infections in the body. Infections are caused by germs such as bacteria, viruses, or fungi. When white blood cell numbers are low or the cells are weak, the body cannot fight infections. For this reason, all BMT patients take drugs to prevent infection by these germs.
One type of infection that is possible in BMT patients is called an invasive fungal disease (IFD), a type of fungal infection that has the ability to spread throughout the body. When fungi enter into blood or other parts of the human body, it is called IFD. IFD is one of the worst forms of infection because the chance of severe sickness and/or death with this type of infection is high. The investigational drug, rezafungin, is being studied to possibly prevent the occurrence of an IFD.

Study objective

The primary objectives are:
* United States Food and Drug Administration (FDA) primary objective
To demonstrate noninferiority in subjects who received an allogeneic BMT for subjects randomized to Rezafungin for Injection compared to subjects randomized to the standard antimicrobial regimen (SAR) for fungal-free survival at Day 90 (±7 days)
* European Medicines Agency (EMA) primary objective
To demonstrate superiority in subjects who received an allogeneic BMT randomized to Rezafungin for Injection compared to subjects randomized to the SAR for fungal-free survival at Day 90 (±7 days)

The secondary objectives are to:

* Evaluate discontinuation of Rezafungin for Injection compared to the SAR secondary to toxicity or intolerance at Day 90 (±7 days)
* Evaluate cumulative incidence of proven and probable invasive fungal disease (IFD) including the number of invasive infections from Candida spp., Aspergillus spp., and Pneumocystis jirovecii in subjects randomized to Rezafungin for Injection compared to the SAR through Day 90 (±7 days)
* Evaluate fungal-free survival in subjects with and without a diagnosis of clinically significant graftversus-host disease (GVHD) who are randomized to Rezafungin for Injection compared to the SAR through Day 90 (±7 days)
* Evaluate time to IFD or death in subjects randomized to Rezafungin for Injection compared to the SAR
* Evaluate overall mortality and attributable mortality, with and without adjustment for patient comorbidity indices, in subjects randomized to Rezafungin for Injection compared to the SAR
* Evaluate the safety and tolerability of Rezafungin for Injection compared to the SAR

The exploratory objectives are to:
* Evaluate fungal-free survival of subjects randomized to Rezafungin for Injection compared to the SAR at Day 14 (±1 day), Day 28 (±1 day), Day 60 (±5 days), and Day 120 (±7 days)
* Evaluate the presence and severity of GVHD in subjects randomized to Rezafungin for Injection compared to the SAR through Day 90 (±7 days)
* Evaluate fungal-free survival in subjects with an underlying diagnosis of acute myeloid leukemia (AML) for subjects randomized to Rezafungin for Injection compared to subjects randomized to the SAR at Day 90 (±7 days)
* Evaluate the incidence of proven, probable, possible, and presumptive IFD (Appendix 4) in subjects randomized to Rezafungin for Injection compared to the SAR at Day 14 (±1 day), Day 28 (±1 day), Day 60 (±5 days), Day 90 (±7 days), and Day 120 (±7 days)
* Evaluate relapse-free survival, with and without adjustment for patient comorbidity indices, in subjects randomized to Rezafungin for Injection compared to the SAR
* Evaluate the PK of Rezafungin for Injection in BMT recipients
* Evaluate post-engraftment cytopenias and transfusion requirements of Rezafungin for Injection compared to the SAR
* Evaluate infections caused by trimethoprim/sulfamethoxazole (TMP/SMX)-sensitive organisms (Toxoplasma gondii [T. gondii], Nocardia spp.) in Rezafungin for Injection compared to the SAR
* Evaluate interruption and discontinuation of antifungal prophylaxis due to suspected IFD of Rezafungin for Injection compared to the SAR
* Evaluate health economic and resource utilization variables, including alternative antifungal and antibiotic therapy of Rezafungin for Injection compared to the SAR

Study design

This is a Phase 3, multicenter, prospective, randomized, double-blind, double-dummy, safety and efficacy study of intravenous (IV) Rezafungin for Injection compared with the current accepted SAR as prophylaxis against IFDs (inclusive of Pneumocystis pneumonia [PCP]) in patients undergoing allogeneic BMT. Subjects will be randomly assigned (2:1 ratio) to receive either Rezafungin for Injection or SAR for prevention of IFD caused by yeasts, molds, and Pneumocystis.

To ensure balance across prophylaxis study drug groups, subjects will be stratified at randomization according
to the following:
* Stratification Factor 1: Underlying disease; AML versus non-AML
* Stratification Factor 2: High risk for IFD and transplant-related mortality (defined as receipt of allogeneic BMT from a mismatched related or unrelated donor, or haploidentical donor) versus low risk for IFD and transplant-related mortality (defined as receipt of an allogeneic BMT from a matched 8/8 related or unrelated donor)

Subjects Randomized to Rezafungin for Injection
Subjects randomized to Rezafungin for Injection will receive a 400 mg loading dose in Week 1, followed by 200 mg once weekly for a total of 13 weeks. The first dose will be administered on Day 0 (±2 days), the second dose on Day 7 (±1 day), followed by once-weekly dosing through the last possible dose administered on Day 84 (±1 day). To maintain the blind, subjects randomized to the Rezafungin for Injection group will receive oral
placebo for SAR azole prophylaxis and oral placebo for SAR anti-PCP prophylaxis in accordance with the respective SAR dosing regimens for each. Oral placebo for SAR azole prophylaxis will be changed to IV placebo in subjects who are switched to a SAR IV regimen.

Subjects Randomized to the Standard Antimicrobial Regimen (SAR)
Subjects randomized to the SAR will receive once daily doses of oral fluconazole for 13 weeks, with the first dose administered on Day 0 (±2 days) and the last possible dose administered on Day 90. Fluconazole may be switched to posaconazole due to acute clinically significant GVHD (Grade II or higher that requires immune suppressive therapy; see Appendix 7), as this diagnosis portends increased risks for invasive aspergillosis; however, subjects who are switched to posaconazole cannot be switched back to fluconazole. Azole-based antifungal therapy (fluconazole or posaconazole) can be switched from daily oral therapy to daily IV therapy at the discretion of the Investigator.
In addition, subjects in the SAR group will receive anti PCP prophylaxis with oral TMP/SMX (80 mg TMP/400 mg SMX) once daily. For subjects who achieve neutrophil engraftment, investigators are to initiate TMP/SMX on Day 30 with the last possible protocol-mandated dose administered on Day 90; however, investigators may start subjects on TMP/SMX within 3 days of neutrophil engraftment if engraftment occurs prior to Day 30. Neutrophil engraftment is defined as 3 consecutive days with an absolute neutrophil count (ANC) *500

cells/mm3 or 2 consecutive days with ANC *1000 cells/mm3. For subjects who do not engraft by Day 30, TMP/SMX may be held until Day 40. If neutrophil engraftment does not occur by Day 40, all study drugs must be discontinued and antifungal prophylaxis should be prescribed per standard of care. During the period of study drug administration, it is allowable for TMP/SMX prophylaxis to be permanently discontinued (eg, for TMP/SMX toxicity) while other prophylactic study drug (azole therapy or rezafungin) is continued. However, if azole or rezafungin prophylaxis is discontinued for >10 days then all study drugs must be discontinued and replaced with standard of care prophylaxis. To maintain the blind, subjects randomized to the SAR group will receive placebo for Rezafungin for Injection IV once weekly for 13 weeks in accordance with the Rezafungin for Injection dosing schedule.

Intervention

Subjects will be randomly assigned (2:1 ratio) to receive either Rezafungin for Injection or SAR for prevention of IFD caused by yeasts, molds, and Pneumocystis.

To ensure balance across prophylaxis study drug groups, subjects will be stratified at randomization according
to the following:
* Stratification Factor 1: Underlying disease; AML versus non-AML
* Stratification Factor 2: High risk for IFD and transplant-related mortality (defined as receipt of allogeneic BMT from a mismatched related or unrelated donor, or haploidentical donor) versus low
risk for IFD and transplant-related mortality (defined as receipt of an allogeneic BMT from a matched 8/8 related or unrelated donor)

Subjects Randomized to Rezafungin for Injection
Subjects randomized to Rezafungin for Injection will receive a 400 mg loading dose in Week 1, followed by 200 mg once weekly for a total of 13 weeks. The first dose will be administered on Day 0 (±2 days), the second dose on Day 7 (±1 day), followed by once-weekly dosing through the last possible dose administered on Day 84 (±1 day). To maintain the blind, subjects randomized to the Rezafungin for Injection group will receive oral placebo for SAR azole prophylaxis and oral placebo for SAR anti-PCP prophylaxis in accordance with the respective SAR dosing regimens for each. Oral placebo for SAR azole prophylaxis will be changed to IV placebo in subjects who are switched to a SAR IV regimen.

Subjects Randomized to the Standard Antimicrobial Regimen (SAR)
Subjects randomized to the SAR will receive once-daily doses of oral fluconazole for 13 weeks, with the first dose administered on Day 0 (±2 days) and the last possible dose administered on Day 90. Fluconazole may be switched to posaconazole due to acute clinically significant GVHD (Grade II or higher that requires immune suppressive therapy; see Appendix 7), as this diagnosis

portends increased risks for invasive aspergillosis;
however, subjects who are switched to posaconazole cannot be switched back to fluconazole. Azole-based antifungal therapy (fluconazole or posaconazole) can be switched from daily oral therapy to daily IV therapy at the discretion of the Investigator. In addition, subjects in the SAR group will receive anti-PCP prophylaxis with oral TMP/SMX (80 mg TMP/400 mg SMX) once daily. For subjects who achieve neutrophil engraftment, investigators are to initiate TMP/SMX on Day 30 with the last possible protocol-mandated dose administered on Day 90; however, investigators may start subjects on TMP/SMX within 3 days of neutrophil engraftment if engraftment occurs prior to Day 30. Neutrophil engraftment is defined as 3 consecutive days with an absolute neutrophil count (ANC) *500 cells/mm3 or 2 consecutive days with ANC *1000 cells/mm3. For subjects who do not engraft by Day 30, TMP/SMX may be held until Day 40. If neutrophil engraftment does not occur by Day 40, all study drugs must be discontinued, and antifungal prophylaxis should be prescribed per standard of care. During the period of study drug administration, it is allowable for TMP/SMX prophylaxis to be permanently discontinued (eg, for TMP/SMX toxicity) while other prophylactic study drug (azole therapy or rezafungin) is continued. However, if azole or rezafungin prophylaxis is discontinued for >10 days then all study drugs must be discontinued and replaced with
standard of care prophylaxis. To maintain the blind, subjects randomized to the SAR group will receive placebo for Rezafungin for Injection IV once weekly for 13 weeks in accordance with the Rezafungin for Injection dosing schedule.

Study burden and risks

The research consists of a sceening period, a treatment period, and a follow-up period.
The screening period lasts a maximum of 14 days, the treatment period lasts about 90 days, depending on how the patient responds to the treatment. After the last treatment the patient will come back for a follow-up visit/telephone call.

In total the patient comes to the hospital about 18 times.
The following tests and procedures will take place during the various visits:
1x medical history check, 16x physical examination, 5x neurological examination, 2x ECG, CT scan when required, 18x blood collection, 4x pregnancy test (if applicable), 18x assessing side effects and use of medication, 15x administration of study medication.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Subjects must meet ALL the following inclusion criteria to qualify for the study:
1. Willing and able to provide written informed consent.
2. Males or females *18 years of age.
3. Receiving a human leukocyte antigen (HLA) matched allogeneic peripheral BMT from a family or unrelated donor, HLA-mismatched related or unrelated donor, or haploidentical donor.
4. Diagnosed with 1 of the following underlying diseases:
a. Acute myeloid leukemia (AML), with or without a history of myelodysplastic syndrome, in first or second complete remission.
b. Acute lymphoblastic leukemia, in first or second complete remission.
c. Acute undifferentiated leukemia in first or second remission.
d. Acute biphenotypic leukemia in first or second complete remission.
e. Chronic myelogenous leukemia in either chronic or accelerated phase.
f. One of the following myelodysplastic syndrome(s) defined by the following:
i. Refractory anemia.
ii. Refractory anemia with ringed sideroblasts.
iii. Refractory cytopenia with multilineage dysplasia.

iv. Refractory cytopenia with multilineage dysplasia and ringed sideroblasts.
v. Refractory anemia with excess blasts * 1 (5*10% blasts).
vi. Refractory anemia with excess blasts * 2 (10*20% blasts).
vii. Myelodysplastic syndrome, unclassified.
viii. Myelodysplastic syndrome associated with isolated del (5q).
ix. Chronic myelomonocytic leukemia.
g. Lymphoma (including Hodgkin*s) with chemosensitive disease (i.e., response to chemotherapy) and receiving a related donor transplant.
h. Aplastic anemia.
i. Primary or secondary myelofibrosis.
5. Receiving myeloablative or reduced-intensity conditioning regimens.
6. Adequate renal and hepatic function, within 6 weeks of initiation of conditioning, as measured by:
a. Hepatic (within 72 hours of Day 0): alanine aminotransferase <5× upper limit of normal (ULN) and total serum bilirubin <2.5 mg/dL.
b. Renal (within 72 hours of Day 0): Serum creatinine within normal range for age or if serum creatinine above ULN range for age, a creatinine clearance [CrCl]) *60 mL/min.
7. Baseline blood samples drawn for serum Platelia galactomannan enzyme immunoassay (GM EIA) and *-D glucan levels within 14 days before randomization, with results available prior to randomization.
8. Baseline Toxoplasma serologies available within 6 weeks prior to randomization.
9. Baseline glucose-6-phosphate dehydrogenase (G6PD) deficiency testing with no evidence of G6PD deficiency performed within 6 weeks prior to randomization.
10. Female subjects of child-bearing potential <2 years post-menopausal must agree to and comply with using 1 barrier method (e.g., female condom with spermicide) plus one other highly effective method of birth control (e.g., oral contraceptive, implant, injectable, indwelling intrauterine device, vasectomized partner), or sexual abstinence while participating in this study. Male subjects must be vasectomized, abstain from sexual intercourse, agree to use barrier contraception (condom with spermicide), and also agree not to donate sperm while participating in the study and for 120 days from the last IV dose of study drug.

Exclusion criteria

1. Diagnosis of AML not in morphological remission.
2. Diagnosis of chemotherapy-resistant lymphoma.
3. Suspected or diagnosed IFD within 4 weeks of screening.
4. Diagnosed symptomatic heart failure with left ventricular ejection fraction (LVEF) at rest *40%,
LVEF >40% but fails to improve with exercise, or shortening fraction *26%.
5. Personal or family history of Long QT interval on ECG (QT) syndrome or a prolonged QT interval

corrected (QTc) interval (>470 msec in males and >480 msec in females); or concurrent administration of terfenadine, cisapride, astemizole, erythromycin, pimozide, quinidine or halofantrine (Appendix 6A)
6. Diagnosed reduced lung function with either diffusion capacity (corrected for hemoglobin), forced
expiratory volume 1, forced vital capacity *45% of predicted value, or O2 saturation *85% on room air.
7. Suspected or documented PCP within 2 years of screening.
8. Positive baseline serum Platelia GM EIA (* 0.5) and/or *-D glucan assay (*80 pg/mL).
9. Receipt of previous allogeneic BMT.
10. Planned receipt of cord blood for transplantation.
11. Planned peripheral blood or marrow autograft.
12. Underlying diagnosis of multiple myeloma.
13. Grade 2 or higher ataxia, tremor, motor neuropathy, or sensory neuropathy, per National Cancer Institute
(NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
14. History of severe ataxia, neuropathy, or tremors; or a diagnosis of multiple sclerosis or a movement
disorder (including Parkinson*s disease or Huntington*s disease).
15. Planned or ongoing intake at screening of a known neurotoxic medication (see Appendix 5) or a medication or supplement known to severely interact with fluconazole, posoaconazole, or TMP/SMX (see Appendix 6B, Appendix 6C, or Appendix 6D, respectively).
16. Known hypersensitivity to Rezafungin for Injection, any echinocandin, fluconazole, posaconazole, other
azole antifungal, or to any of their excipients.
17. Known hypersensitivity or inability to receive TMP/SMX or any of its excipients.
18. Recent use of an investigational medicinal product within 28 days of the first dose of prophylactic study
drug or presence of an investigational device at the time of screening.
19. Known infection with human immunodeficiency virus (HIV).
20. Pregnant or lactating females.
21. The Principal Investigator (PI) determines that the subject should not participate in the study.
22. Considered unlikely to follow up for 90 days after receipt of the BMT due to logistic concerns
(i.e., location relative to transplant center).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	38
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Rezafungin for Injection
Generic name:	Rezafungin for Injection

Ethics review

Approved WMO Date:	07-01-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-04-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-004981-85-NL
CCMO	NL68463.091.19