A Phase III, adjudicator-blinded, randomised study to evaluate the efficacy and safety of treatment with olorofim versus treatment with AmBisome® followed by standard of care (SOC) in patients with invasive fungal disease (IFD) caused by Aspergillus species

Published: 29-09-2021
Last updated: 25-09-2024

This study has been transitioned to CTIS with ID 2024-513030-38-00 check the CTIS register for the current data. To compare ACM at Day 42 following treatment with olorofim versus treatment with AmBisome® followed by SOC in the intent-to-treat (ITT)…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Fungal infectious disorders
Study type	Interventional

Summary

ID

NL-OMON56006

Source
ToetsingOnline

Brief title
F901318/0041
OASIS
Olorofim in Aspergillus Infection Study

Condition

- Fungal infectious disorders

Synonym
fungal infections on other places than skin or mucous membranes, invasive fungal infections due to Aspergillus species

Research involving
Human

Sponsors and support

Primary sponsor: F2G Ltd.
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: Aspergillus, F901318, invasive fungal infections, Olorofim

Outcome measures

Primary outcome

All cause mortality rate at Day 42 in the ITT population

Secondary outcome

• Compare the treatment effects with olorofim vs AmBisome® followed by SOC on

DRC adjudicated assessment of overall outcome in patients with IA at Day 42,

84, and EOT.

• Compare the treatment effects with olorofim versus treatment with AmBisome®

followed by SOC on:

- Investigator-assessed overall response at Day 14, 28, 42, 84, EOT, and FU

- Galactomannan index at Day 14, 28, 42, 84, EOT, FU

- All cause mortality at Day 84

- Survival time

- Data Review Committee attribution of mortality to IA at Day 42 and 84

- Diagnosis of a secondary fungal infection at any time through EOT

- Quality of life as measured by the 5 Level 5 Dimension (EQ-5D-5L) at

Baseline, Days 14 and EOT

• To assess the safety and tolerability of treatment with olorofim relative to

AmBisome® followed by SOC up to Day 84 and FU visits

• To collect olorofim systemic exposure data for population PK modelling and to

collect H26C metabolite systemic exposure data in certain geographical regions

• To collect health variables

Study description

Background summary

Invasive fungal (IA) infections due to resistant fungi cause substantial morbidity and mortality when either not treated or when available therapy lacks activity, especially in patients with reduced immune function. Invasive aspergillosis in immunocompromised patients is a devastating illness with a mortality that approaches 100% without effective therapy. Timely treatment of IA with an effective modern drug may reduce mortality to approximately 20% at 6 weeks. When IA is resistant or becomes resistant to the azole antifungal agents, mortality rates range between 50% and 100%, mortality rates that approach those for untreated infection. The emergence of resistance threatens the future use of the azoles and highlights the urgent need for new and effective antifungal agents.
In addition to the emergence of resistance, currently available classes of antifungal treatment are limited by dosage forms, drug-drug interactions, and significant adverse reactions.

Based on the nonclinical efficacy profile and on preliminary results of an ongoing Phase IIb study, olorofim may offer an effective treatment for patients with IA. The present study is designed to compare the efficacy, safety, and tolerability of olorofim with that of AmBisome® followed by guideline-based hierarchy standard of care (SOC) in patients with IA whose infection is either refractory to or unsuitable for azole therapy.

Study objective

This study has been transitioned to CTIS with ID 2024-513030-38-00 check the CTIS register for the current data.

To compare ACM at Day 42 following treatment with olorofim versus treatment with AmBisome® followed by SOC in the intent-to-treat (ITT) population of patients with IFD caused by proven IA at any site or probable lower respiratory tract disease (LRTD) Aspergillus species.

Study design

A Phase III, adjudicator-blinded, randomised study to evaluate the efficacy and safety of treatment with olorofim versus treatment with AmBisome® followed by standard of care (SOC) in patients with invasive fungal disease (IFD) caused by Aspergillus species.

Intervention

Subjects will be randomized 2:1 to olorofim versus AmBisome® .

Olorofim:
Treatment: Oral intake of 30mg coated tablets

starting dose: 150 mg (5 tablets) taken twice for 1 day
maintenance dose: 90 mg (3 tablets), taken twice per day for up to 12 weeks
Both the starting and maintenance doses will be taken every 12 hours

The maximum dose is 150 mg (5 tablets) taken every 12 hours

AmBisome®:
Treatment: intravenously, 3mg AmBisome® per kilogram of bodyweight once per day for at least 10 days

Study burden and risks

The length of subject participation in this study will depend on if and how quickly the infection responds to the medication given in this study. The maximum duration of participation is expected to be approximately 18 weeks. Subjects will have up to 18 study visits during the study. If the infection clears up during the treatment period, subject participation will be shorter, and there will be fewer study visits. A visit will take up to 6 hours.

Subjects will need to come to the hospital more often than they would usually, and have additional tests. These include physical examination, X-ray/CT/MRI

imaging, ocular assessment, ECGs, pregnancy tests, urine tests and blood tests. Collection of a small piece of the infected area or fluid from the infected area to determine which fungus is causing your infection, possibly there will be a bronchoscopic assessment if the infection is in the lungs. Subjects will be asked to complete questionnaires and fill a patient dosing diary. Subjects must avoid pregnancy. Subjects must be careful when driving or using machines (due to the risk of dizziness). Participants who agree to take part in the ECG sub-study, will be asked to wear a device called a Holter monitor at certain time points during the main study.

Risk of side effects. The following side effects that were reported by some healthy subjects who received the study drug as multiple oral doses during the studies: Dizziness, Nausea or feeling sick, Increased liver enzymes, Back pain, Throat irritation or pain, Diarrhea , Upper respiratory tract infection, Dry skin, Blurred vision, Stomach pain or bloating, Constipation, Dry lips, Vomiting or being sick, Chest pain, Symptoms of influenza, Bruising, Pain when urinating , Rash, Arm or leg pain, Feeling tired, Blocked nose. In addition, the risk associated with exposure to X-rays.

Side effects of AmBisome®
Low magnesium, calcium, or sodium blood levels, leading to feeling tired, confused, muscle weakness or cramps ,High blood sugar levels
Headache ,A faster heart rate than normal, Widening of the blood vessels, causing low blood pressure and flushing, Breathlessness, Diarrhea, Stomach pain, Rash , Chest pain , Back pain, Abnormal results for liver or kidney function showing up in blood tests or urine tests

Based on the nonclinical efficacy profile and on preliminary results of an ongoing Phase IIb study, olorofim may offer an effective treatment for patients with IA.

Contacts

Public
F2G Ltd.

Lankro Way -
Eccles, Manchester M30 0LX
GB
Scientific
F2G Ltd.

Lankro Way -
Eccles, Manchester M30 0LX
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Male and female patients ages >= 18 years and weighing >= 30 kg, [*] or Patients unable to write and/or read but who fully understand the oral information given by the Investigator.
2. Patients with proven IA at any site or probable LRTD IA per EORTC/MSG 2019 criteria as adapted for this study (see Appendix 2) and where the duration of specific therapy for this episode of IA has been <= 28 days. For purposes of this inclusion, the duration of specific therapy includes any mould-active therapy given for this episode of IA whether subsequently judged potentially effective or not.
3. Patients requiring therapy with an antifungal agent other than a mould-active azole and who have had <= 96 hours of potentially effective prior therapy. Potentially effective prior therapy includes any agent to which the infecting strain of Aspergillus is likely to be susceptible. There are no exclusions or limitations on such agents (eg, AmBisome® is permitted) other than their duration.
Patients must meet at least one of these criteria:
a) Proven or suspected azole resistance in patients who have had <= 96 hours of potentially effective prior therapy [*]
b) Breakthrough infection on triazole prophylaxis: patients who have had any duration of prophylaxis prior to the breakthrough but <= 96 hours of potentially effective prior therapy.
c) Any other medical reason an azole is inappropriate for the patient at screening. In all cases, patients must have had <= 96 hours of potentially effective prior therapy

(potential for drug-drug interaction, previous history of azole intolerance)
d) Invasive aspergillosis refractory to triazole therapy in patients who have had <= 28 days of prior therapy where refractory IA was defined per an international expert meeting report
4. AmBisome® is an appropriate therapy for the patient.
a) For avoidance of doubt, prior therapy with an amphotericin B (eg, AmBisome® or other) is not an exclusion provided that such prior therapy does not exceed the rules for maximum duration of potentially effective prior therapy discussed as part of Inclusion Criterion 3.
5. Ability and willingness to comply with the protocol.
6. Female patients must be non-lactating and at no risk of pregnancy [*]
7. Male patients with female partners of childbearing potential must either totally abstain from sexual intercourse or use a highly effective means of contraception.
For more details, please refer to the protocol.

Exclusion criteria

1. Women who are pregnant or breastfeeding.
2. Known history of allergy, hypersensitivity, or any serious reaction to any component of the study drug (olorofim or AmBisome®).
3. Patients with only chronic aspergillosis, aspergilloma or allergic bronchopulmonary aspergillosis.
4. Suspected mucormycosis (zygomycosis). Evidence for the presence of olorofim non susceptible filamentous fungi such as Mucorales should be urgently followed up. Increased vigilance for the possibility of mucormycosis (zygomycosis) is required for suspected IA with negative baseline GM.
5. Patients with a known active second fungal infection of any type, other than candidiasis being treated with fluconazole.
6. The requirement for ongoing use of echinocandin as Candida prophylaxis (for avoidance of doubt, prior use of an echinocandin is permitted; if ongoing prophylaxis for Candida is needed, then fluconazole must be an acceptable choice [see Section 5.8.4.1, discussion of concomitant antifungal agents]).
7. Microbiological findings (eg, bacteriological, virological) or other potential conditions that are temporally related and suggest a different aetiology for the clinical features.
8. Patients with human immunodeficiency virus (HIV) infection who are currently not receiving antiretroviral therapy. Patients with HIV infection receiving antiretroviral therapy can participate in the study. In cases where HIV infection is first diagnosed at the same time as the invasive fungal infection, if antiretroviral therapy is commenced at the time of enrolment, then such patients are eligible for enrolment.
9. Any known or suspected condition of the patient that may jeopardize adherence to the protocol requirements or impede the accurate measurement of efficacy (eg, neutropenia not expected to resolve, patients with uncontrolled

malignancy who are treatment refractory and receiving only palliative therapy).
10. with a concomitant medical condition that, in the opinion of the Investigator, may be an unacceptable additional risk to the patient should he/she participate in the study.
11. Patients previously enrolled in a study with olorofim/F901318.
12. Treatment with any investigational drug in any clinical trial within the 30 days prior to the first administration of study drug except for unblinded protocols (eg, open-label oncological regimen variations or biologic studies). Prior to enrolling patients who are on other open label studies it is the site's responsibility to ensure that the study criteria for that study allow for enrolment into this study.
13. Patients receiving treatment limited to supportive care due to predicted short survival time.
14. Patients with a baseline prolongation of Fridericia's Correction Formula (QTcF) >= 500 msec, or at high risk for QT/QTc prolongation.
15. Evidence of hepatic dysfunction with any of the following abnormal laboratory parameters at screening (for avoidance of doubt, liver transplant recipients may be enrolled if their laboratory parameters do not meet the exclusions):
a) Total bilirubin >= 2 × upper limit of the normal range (ULN)
b) Alanine transaminase or aspartate transaminase (AST) >= 3 × ULN
c) Patients with known cirrhosis or chronic hepatic failure (regardless of ALT/AST/total bilirub
16. Prohibited concomitant medications: concomitant administration of inhibitors of human DHODH (teriflunomide and leflunomide) are prohibited. There are currently no other absolutely prohibited concomitant medications or vaccines, but there are medications with potentially significant DDIs, and the management of potential interactions should be considered before study enrolment.
17. Additional exclusion criteria required by local regulatory authorities.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-07-2023
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AmBisome
Generic name:	Amphotericin B
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	N/A
Generic name:	Olorofim

Ethics review

Approved WMO Date:	29-09-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-02-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-09-2023
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-10-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-02-2024
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
EU-CTR	CTIS2024-513030-38-00
EudraCT	EUCTR2021-000386-32-NL
CCMO	NL78860.091.21