An open-label single-arm Phase IIb study of F901318 as treatment of invasive fungal infections due to Lomentospora prolificans, Scedosporium spp., Aspergillus spp., and other resistant fungi in patients lacking suitable alternative treatment options.

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Primary:• Describe the Data Review Committee (DRC)-adjudicated efficacy of F901318 as treatment for infections due to resistant fungi in patients lacking suitable alternative treatment options.Secondary:• Describe the safety of F901318 as treatment...

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

Summary

ID

NL-OMON52686

Source
ToetsingOnline

Brief title
FORMULA-OLS:F901318

Condition

- Fungal infectious disorders

Synonym
invasive fungal disease(IFD), invasive fungal infections

Research involving
Human

Sponsors and support

Primary sponsor: F2G Biotech GmbH (FN 483749 x)
Source(s) of monetary or material Support: Industry

Intervention

Keyword: F901318, invasive fungal infections, open-label single-arm, Phase IIb

Outcome measures

Primary outcome

Primary Endpoint:

• DRC-adjudicated overall response rate by pathogen at Day 42.

Secondary outcome

Efficacy Endpoints:

Secondary Endpoints (all by pathogen and also in aggregate)

• DRC-adjudicated overall response at Day 7, Day 14, Day 28 main study phase,

EOT, Day 84 and 4-week FU*.

• DRC-adjudicated and Investigator-assessed clinical response at Day 7, Day 14,

Day 28, Day 42 main study phase, EOT, Day 84 and 4-week FU*.

• Where appropriate for the IFD, radiological response at Day 7, Day 14, Day

28, Day 42 main study phase, EOT, Day 84 and 4-week FU*.

• DRC-adjudicated and Investigator-assessed mycological response by pathogen

and by susceptibility category at Day 7, Day 14, Day 28, Day 42 main study

phase, EOT, Day 84 and 4-week FU*.

• Investigator-assessed overall response (integration of clinical,

radiological, and mycological response) at Day 7, Day 14, Day 28, Day 42 main

study phase, EOT, Day 84 and 4-week FU*.

• All-cause mortality at Day 42 main study phase, EOT, Day 84 and 4-week FU*.

In addition, overall survival (median time

to death) will be presented.

Patients with complete clinical response to study drug treatment will also be evaluated for relapse of the treated IFD and for newly emergent IFD at selected study visits up to the main study phase EOT visit (Day 84 to Day 90).

• If deemed relevant, the aforementioned endpoints may also be summarised by subgroups judged relevant (e.g., the subgroup of subjects who continued therapy beyond Day 90 and who thus have only a single combined EOT visit encompassing Day 84 and EOT).

•Change from baseline during treatment in ECG measured by Holter monitor in a subset of patient (to be reported separately)

*For patients planning to receive ET beyond Day 90, the Day 84 visit and the main study phase EOT visit will be combined into a single Day 84 / EOS / EOT visit on approximately Day 90 and there will be no 4-week FU visit in the main study phase.

Safety:

• Overall incidence of: - AEs. - Serious AEs (SAE) (including deaths). - AEs leading to premature treatment discontinuation. - AEs leading to premature

study withdrawal. - AEs by relationship. - AEs by severity (common terminology criteria for adverse event [CTCAE] grade). - AEs of Special Interest (AESI).

• Changes from baseline during the treatment period and at FU in: - Vital signs (including weight and body mass index [BMI]). - Clinical laboratory assessments and incidence of pre-defined abnormalities. - Electrocardiogram (ECG) results and incidence of pre-defined abnormalities. - Physical examination findings.

• Ophthalmology: external eye exam.

• Changes in concurrent medication dose and/or frequency resulting from potential DDIs.

• Overall exposure, individual dose modification, dose intensity.

Pharmacokinetics:

• PK data (Cmin; Cmax, Tmax, AUC 0-*au, CL/F and Vz/F).

• Effect of concomitant medication on PK profiles.

Study description

Background summary

Invasive fungal infections are a growing clinical concern in many settings but are especially common in immunocompromised patients, can involve any part of the body, and are associated with high mortality rates. Current treatment has limitations including limited dosage forms, DDIs, significant adverse reactions and resistance.There is a critical medical need for an antifungal agent with a novel mechanism of action and with high efficacy against a broad spectrum of fungal species (Section 2.1.1. protocol). Such an agent would have added value if it were effective by both intravenous (IV) and oral routes of administration, was well tolerated, and had a limited potential for DDIs. In addition, a predictable and reliable PK profile would allow well controlled

therapy. F901318 is the first of a new class of antifungal agents with a novel, well defined mechanism of action, inhibiting a rate limiting enzyme of fungal pyrimidine biosynthesis, DHODH. Based on the nonclinical efficacy profile, F901318 may offer an effective treatment in patients with a diverse selection of fungal infections. In clinical pharmacology studies, F901318 has been well tolerated when administered at dosages which provide sustained systemic exposure within the predicted therapeutically effective range. The present study is designed to evaluate the safety, tolerability and efficacy of F901318 in patients with IFDs caused by Aspergillus spp, Scedosporium spp. and other fungal species for which there are limited treatment options available.

Study objective

Primary:
• Describe the Data Review Committee (DRC)-adjudicated efficacy of F901318 as treatment for infections due to resistant fungi in patients lacking suitable alternative treatment options.
Secondary:
• Describe the safety of F901318 as treatment for infections due to Lomentospora prolificans, Scedosporium spp., Aspergillus spp., and other resistant fungi in patients lacking suitable alternative treatment options.
• Describe the efficacy of F901318 in terms of Investigator-assessed overall response (integrating clinical, radiological and mycological response).
• Describe all-cause mortality.
• Characterize pharmacokinetics (PK) of study drug and metabolite(s) including effects of dose adaptations.
• Evaluate dose adaptation and drug-drug interaction (DDI) management strategies.
• Evaluate the F901318 plasma concentration-QTc relationship by providing data from time-matched PK samples and Holter ECG recordings
(to be reported separately)

Study design

Open-label, single-arm

Intervention

Treatment: Oral intake of 30mg coated tablets

Dose:

starting dose: 4 mg per kg per day
maintenance dose: 2.5 mg per kg per day
Every 8-12 hours

Max. daily dose is 300mg

Study burden and risks

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, ECGs, pregnancy tests, urine tests and blood tests. Possibly there will be a bronchoscopic assessment if the infection is in the lungs. Subjects must avoid pregnancy. Subjects must be careful when driving or using machines (due to the risk of dizziness). Consenting patients participating in the ECG substudy will complete the visits and assessments as described in the protocol. In addition, Holter ECG recordings will be conducted at a baseline visit and on the day of Intensive PK sampling.

There is the 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: blurred vision, diarrhea, nausea, increased liver enzymes, headache, dizziness and throat irritation or pain. In addition, there is the risk associated with exposure to X-rays.

Inclusion of patients in this trial is based on the lack of suitable alternative treatment options to them.
Based on the nonclinical efficacy profile, F901318 may offer an effective treatment in patients with a diverse selection of fungal infections. In clinical pharmacology studies, F901318 has been well tolerated when administered at dosages which provide sustained systemic exposure within the predicted therapeutically effective range.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male and female patients aged at least 18 years or male and female patients aged 16 years or 17 years and who weigh at least 40 kg who have been fully informed and who have given voluntary written informed consent, or whose legally authorized representative(s) have been fully informed and have given voluntary written informed consent if applicable and in compliance with local regulations, OR: Patients unable to write and / or read but who fully understand the oral information
given by the Investigator who have given oral informed consent witnessed in writing by an independent person and in compliance with local regulations., 2. Ability and willingness to comply with the protocol.,3. Female patients must be non-lactating and at no risk of pregnancy for one of the following criteria:, a. Postmenopausal for at least 1 year;, b. Post-hysterectomy and/or post-bilateral ovariectomy;, c. Of childbearing potential, with a negative urine or serum human chorionic gonadotropin pregnancy test at the Screening visit and must be using a highly effective method of birthcontrol throughout the course
of the study period:
i) Established use of oral, injected, transdermal, intravaginal or implanted hormonal methods of contraception associated with inhibition of ovulation
ii) Placement of an intrauterine device or intrauterine hormone-releasing system
iii) Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate
iv) Bilateral tubal occlusion
v) Sexual abstinence (reliable sexual abstinence is acceptable but

periodic abstinence [e.g. calendar, ovulation, symptom-thermal, or post ovulation methods] and withdrawal are not acceptable)., 4. Male patients with female partners of childbearing potential must either totally abstain from sexual intercourse or use a highly effective means of contraception throughout study participation and agree to continue its use for 30 days after stopping study drug., 5. Patients with one of these 4 forms of invasive fungal infection confirmed by culture or other diagnostic (as agreed with the MM):, a) Lomentospora (Scedosporium) prolificans (LoPro),, b) Scedosporium spp.,, c) Aspergillus spp.,, d) Other F901318-susceptible fungi (as described in the IB or based on information provided by the MM, and in either case requiring approval of the MM),, OR, e) Probable LRTD IA based on EORTC/MSG criteria (Appendix 2) but not meeting the criteria for culture proven invasive fungal infection.
*For further details on inclusion criterium 6, see the protocol footnote, 6. Patients will also have limited alternative treatment options based on meeting one or more of the following criteria:, a) Known or predicted resistance of the infecting isolate to all licensed agents. LoPro automatically meets this criterion - other fungi may qualify after discussion with the MM,, b) Failure of available therapy. Failure to improve based on clinical or radiologic grounds despite receiving >=7 days of standard antifungal treatment AND alternative licensed agents are either predicted to be ineffective or are contraindicated,, c) Intolerance to available therapy. Current therapy cannot be continued due to therapy-related adverse reactions (e.g., increase in serum creatinine above upper limit of normal with an amphotericin, persistent visual disturbances with voriconazole, allergic reaction with any compound, or other recognized drug-related AE) AND alternative licensed agents are either predicted to be ineffective or are contraindicated, d) Inability to manage DDIs. Inability to continue current therapy due to DDIs that cannot be managed AND alternative licensed agents are either predicted to be ineffective or are contraindicated,, e) Inability to produce therapeutic drug levels. Inability to produce or maintain therapeutic blood levels with current therapy AND alternative licensed agents are either predicted to be ineffective or are contraindicated, f) An IV-only option (e.g., an amphotericin) has produced a clinical response AND it is standard practice to switch to an oral azole for completion of therapy AND at least one of the following is true:, i) Azole-resistance is known based on susceptibility testing of the infecting isolate,, ii) Azole-resistance is predicted by PCR or similar molecular diagnostic tool,, iii) Azole-resistance is suspected based on epidemiological or clinical grounds (e.g., development of aspergillosis while on mould-active azole prophylaxis; history of lack of response to a mould-active azole at an early point in the therapeutic course),, iv) An azole would be acceptable therapy but it is known or predicted that unmanageable DDIs will occur, g) Other MM agreed inclusion. Patient does not meet any of criteria a) to f), but treatment with F901318 is judged appropriate by the investigator. Inclusion of patients based on this category must be agreed with the MM and the rationale must be documented.
Inclusion Criteria for Extended Treatment Phase

1. Patient has completed 84 to 90 days of treatment with F901318 in the main study phase.
2. In the Investigator's opinion the patient has potential to continue to benefit from extended treatment with F901318. The Investigator must discuss ET with the MM, and the MM must approve ET for each patient.
3.No other alternative treatment option is available.
4. Patient is willing to give informed consent for ET.
5. Patient is willing and able to comply with monthly visits to the clinic for assessments.

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., 3. Patients with chronic aspergillosis, aspergilloma or allergic bronchopulmonary aspergillosis., 4. Suspected zygomycosis (mucormycosis) as the IFD used to quality for the study. Evidence for the presence of F901318 non-susceptible filamentous fungi such as Mucorales should be urgently followed up. Increased vigilance for the possibility of zygomycosis is required for suspected IA with negative baseline GM., 5. Microbiological findings (e.g., virological) or other potential conditions that are temporally related and suggest a different etiology for the clinical features., 6. HIV infection but not currently receiving antiretroviral therapy.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 enrollment, then such patients are eligible for enrollment., 7. Any known or suspected condition of the patient that may jeopardize adherence to the protocol requirements or impede the accurate measurement of efficacy (e.g. neutropenia not expected to resolve, patients with uncontrolled malignancy who are treatment refractory and receiving only palliative therapy)., 8. Patients 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., 9. Patients previously enrolled in a study with F901318., 10. 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 (e.g. open-label oncological regimen variations or biologic studies). Prior to enrolling patients that 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., 11. Patients receiving treatment limited to supportive care due to predicted short survival time., 12. Patients with a baseline prolongation of QTcF >=500 msec, or at high risk for QT/QTc prolongation, e.g.a) A family history of long QT syndrome, b) Other known pro-arrhythmic conditions, c) Risk factors for Torsade de Pointes (e.g. uncompensated heart failure, abnormal plasma potassium or magnesium levels that cannot be corrected, an unstable cardiac condition during the last 30 days).,

13. Evidence of hepatic dysfunction with any of the following abnormal laboratory parameters at Screening:, a) Total bilirubin >=2 x ULN, b) Alanine transaminase or aspartate transaminase >=3 x ULN, c) Patients with known cirrhosis or chronic hepatic failure, 14. Prohibited concomitant medications. Concomitant administration of inhibitors of human DHODH (teriflunomide and leflunomide) is prohibited. There are currently no other absolutely prohibited concomitant medications but there are medications with potentially significant DDIs and the management of potential interactions should be considered before study enrollment (Section 5.9.1)., 15. Additional exclusion criteria required by local regulatory or legal order.
- Prisoners or subjects who are legally institutionalized.
- Patients who are not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or patients potentially at risk of noncompliance to study procedures.
- Patients who are dependent on the Sponsor or Investigator or who are deemed vulnerable for any reason.
- Patients who are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.
- Any specific situations during study implementation/course that may raise ethics consideration.
Exclusion Criteria for Extended Treatment Phase
1. Patients who are not suitable for the participation in the ET phase, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or patients potentially at risk of noncompliance to study procedures.
Patients who are unwilling or unable to continue the contraceptive measures as described for the main study phase.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-07-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	F901318
Generic name:	F901318

Ethics review

Approved WMO Date:	21-06-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-07-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-08-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-11-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-11-2018
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-02-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-06-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-06-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-10-2020
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-03-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-11-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-01-2023
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	EUCTR2017-001290-17-NL
CCMO	NL65316.091.18