**Clinical trial protocol**

**Clinical trial protocol number:** F901318/0032

**Protocol Title:** 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

**NCT number**: NCT03583164

**Document date**: 28 February 2020

# Clinical Study Protocol

| | |
|---|---|
| **Protocol Title:** | **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.** |
| **Working title:** | **FORMULA-OLS: F901318, the first orotomide for invasive fungal diseases - an open-label single-arm study.** |
| **Protocol Number:** | **F901318/0032** |
| **Date of Original Protocol:** | **19 December 2017** |
| **Date of Protocol Amendment 01** | **24 January 2018** |
| **Date of Protocol Amendment 01-01** | **07 March 2018** |
| **Date of Protocol Amendment 02** | **02 May 2018** |
| **Date of Protocol Amendment 03** | **28 November 2018** |
| **Date of Protocol Amendment 04** | **03 May 2019** |
| **Date of Protocol Amendment 05** | **30 October 2019 (not implemented)** |
| **Date of Protocol Amendment 06** | **28 February 2020 (updated from Amendment 04)** |
| **Product:** | **F901318** |
| **Product INN:** | **Olorofim** |
| **IND No.:** | [redacted] |
| **EudraCT No.:** | **2017-001290-17** |
| **Study Phase:** | **IIb** |
| **Sponsor:** | **F2G Biotech GmbH (FN 483749 x)**<br>**Seilerstätte 17/13**<br>**1010 Vienna**<br>**Austria** |

**Project Manager:**

**Study Monitor:**

**Medical Adviser:**

**Principal Investigator:** **Sharon Chen FECMM**
**Centre for Infectious Disease and Microbiology**
**Westmead Hospital and the University of Sydney,**
**Darcy Road**
**Westmead, NSW 2145, Australia**

Confidentiality Statement

This confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

# Sponsor Signature

**PROTOCOL TITLE:** 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.

**PROTOCOL NO:** F901318/0032

**PROTOCOL VERSION:** Amendment 06

[redacted]

# Protocol Amendment Summary of Changes

## Document History

| Document | Date | Substantial | Region |
|---|---|---|---|
| Amendment 06[a] | 28 February 2020 | Yes | Global |
| Amendment 05[b] (not implemented) | 30 October 2019 | Yes | Global |
| Amendment 04 | 03 May 2019 | Yes | Global |
| Amendment 03 | 28 November 2018 | Yes | Global |
| Amendment 02 | 02 May 2018 | Yes | Global |
| Amendment 01-01 | 07 March 2018 | Yes | Local (Belgium) |
| Amendment 01 | 24 January 2018 | Yes | Global |
| Original Protocol | 19 December 2017 | - | - |

a: Changes introduced to Amendment 05 which are relevant to Amendment 06 are included in the Summary of Changes for Amendment 06.

b: Amendment 05 was signed by the Sponsor and by the Principal Investigator but was not implemented. Amendment 05 was not submitted to any Regulatory Authorities or Ethics Commitees, nor was it circulated to any study centres.

## Amendment 06 28 February 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

### Overall Rationale for Amendment 06

The number of patients and number of centres have been increased; the intent is to continue Study 32 in parallel with a Phase III study, such that patients who have no suitable treatment options for their invasive fungal disease and are ineligible for the Phase III study will be able to enrol into Study 32 and receive treatment with F901318.

An initial analysis was been added after 100 patient; F901318 has been granted Breakthrough Therapy Designation based on preliminary clinical evidence that demonstrates F901318 may provide substantial improvement over available therapy. As this designation is intended to expedite the development and review of important products, an initial analysis of data will be performed when the first 100 patients have completed treatment, to enable the Sponsor to formally consider the possibility that initial approval might be achievable based on the data for the population of patients with limited or no treatment options for life-threatening fungal infections.

Body-weight adjustment of the F901318 dose has been removed; Population pharmacokinetic (PK) modelling has predicted that use of body weight-adjusted dosing increases the between-patient variability in systemic exposure (as the effect of body weight on F901318 PK is relatively small, dose adjustment by body weight tends to overcompensate). As a

consequence, all patients will start treatment on F901318 with a fixed dosing regimen, unless the use of concomitant medications requires dose adjustment.

Therapeutic drug monitoring (TDM) is being removed [redacted]

The inclusion of 16 year old and 17 year old patients who weigh at least 40 kg has been introduced following requests from study investigators to allow enrolment of patients who are less than 18 years old. [redacted]

**Description of Changes in Amendment 06**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title page | IND number has been added. | The IND number had been omitted previously. |
| Title page | Sponsor address has been updated. | The Sponsor address has changed. |
| Synopsis<br>Section 3.4<br>Section 4.1.1 | Patient-reported outcomes have been added as an endpoint during the extended treatment phase, to be collected by completion of the EQ-5D-5L questionnaire. | This will provide additional insight into the benefits of treatment with F901318. |
| Synopsis;<br>Section 4.1 | The number of patients has been increased to 200, the number of centres has been increased to 100 and the enrolment period has been extended to 60 months. | This allows patients with invasive fungal disease who are ineligible to receive F901318 in a Phase III study to have access to treatment wth F901318. |
| Synopsis;<br>Section 4.1<br>Section 4.2<br>Section 5.1<br>Section 6.5 | The dose is defined as 150 mg twice daily (bid) (loading dose) and 90 mg bid (maintenance dose). A window of ±1 hour has been added to the interval between oral doses. | This details the revised dosing regimen considered to provide greater control of systemic exposure and describes the acceptable variation in the timing of oral doses, as detailed in the Dose Guidance Manual. |
| Synopsis<br>Section 4.1<br>Tables 1 and 2<br>Section 6.5 | Intensive PK day is required [redacted] | The change is for logistical ease (for both study centre and patient) [redacted] |
| Synopsis<br>Section 4.1<br>Section 5.9.1<br>Section 5.9.2<br>Section 6.5 | The unscheduled intensive PK day has been removed. | Arranging an unscheduled intensive PK day was logistically complex, and trough PK samples provide sufficient information on potential drug-drug interactions (DDI). |
| Synopsis<br>Section 4.1<br>Section 5.7<br>Section 6.5 | Reference to TDM and subsequent dose adjustment based upon trough levels has been removed. Trough samples will continue to be collected and will be sent to regional hubs for rapid analysis, but no action will be taken based on the results. | Analysis of all available data to date suggests that TDM with dose adjustment is not a reliable approach [redacted] |
| Synopsis<br>Section 4.1<br>Section 6.6<br>Section 9.4 | A statement has been added to clarify that samples for [redacted] analysis will be taken from approximately 50 patients. | [redacted] samples from 50 patients is expected to be sufficient for the evaluation [redacted] |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis,<br>Section 4.1<br>Section 5.1 | Based on clinical evaluation of efficacy by the Investigator, stepwise increases of maintenance doses of F901318 to 150 mg bid may be permitted, following discussion with the Medical Monitor (MM). | [redacted] |
| Synopsis<br>Section 4.1 | Time of last meal prior to collecting a trough PK sample is to be recorded. | [redacted] |
| Synopsis<br>Section 4.1<br>Section 8.1<br>Section 8.13 | An initial analysis of data will be performed after the first 100 patients have completed the End of Study (EOS) visit for the main phase of the study. | [redacted] |
| Synopsis<br>Section 4.3 | Inclusion criterion 1 has been updated to include patients who are 16 years old or 17 years old and who weigh at least 40 kg. | This update will allow patients who are 16 years old or 17 years old and who weigh at least 40 kg to receive treatment with F901318. It is anticipated that the benefit:risk profile of F901318 is anticipated to be consistent with that observed in adult patients. |
| Section 2.1.3 | A summary is presented for the rationale in place at study start for the use of TDM and $C_{trough}$-based dose adjustment. [redacted] | An overview of the rationale behind the changes for dosing regimens and TDM is required to help the Investigators have a better understanding of how to use F901318 in the clinical setting. |
| Section 4.1 | Clarification of the timings for analysis of liver enzymes and bilirubin. | On review of available data, these timings are considered optimal [redacted] |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Table 1 | [redacted] | Timing of assessements has been optimized. |
| Section 4.2 | [redacted] by using a fixed dose of F901318 [redacted] This replaces the initial approach of body weight-adjusted dose and TDM intended to keep peak plama levels within a target range. | Reflects current thinking on the most suitable measures [redacted] |
| Section 5.1 | Table 4 has been deleted. | [redacted] |
| Section 5.1 | Text has been added to describe the maximum permitted duration of treatment interruption when patients require further treatment with F901318 after a successful overall outcome at the EOT visit. | This clarification will enable the Investigator to provide continued treatment with F901318 if required due to an acute change in clinical status. |
| Section 5.2 | Detail of the oral formulation has been updated. | This update provides additional information relating to F901318 tablets. |
| Section 5.9.1 | Reference to the use of TDM to monitor the impact of dose changes due to a DDI has been removed. | This is consistent with the overall removal of TDM. [redacted] |
| Section 6.4.1<br>Section 6.4.1.2 | [redacted] | Ensures that medically significant hepatic adverse reactions can be reported appropriately to Regulatory Authorities. |
| Section 6.4.1.3 | Requirement for hepatic biochemistry follow up to be extended if requested by the Hepatic Advisory Committee. | This is formal documentation within the protocol of the follow up process which is currently in place. |
| Section 6.4.4.2 | [redacted] | [redacted] |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 8.1 | Sample size calculations in support of the increased number of patients (200) have been included. | Required to support expansion of study. |
| Appendix 3 | Detailed guidance has been added relating to resuming treatment with F901318 [redacted] | This guidance will facilitate consistent management of patients [redacted] |

Further minor changes have been made throughout the protocol to correct typographical errors and to clarify text.

# SYNOPSIS

| | |
|---|---|
| **Name of Sponsor/Company:** | F2G Ltd. |
| **Name of Finished Product:** | Not applicable |
| **Name of Active Ingredient:** | F901318 |
| **Title of Study:** | 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. |
| **Protocol No:** | F901318/0032 |
| **Investigators:** | Multiple |
| **Study Centres:** | Up to 100 centres globally |

**Study Duration:**
The rate of recruitment into the study is expected to be low; the enrolment period will be at least 60 months.

**Phase:**
IIb

**Objectives:**

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 patient-reported outcomes based on the EQ-5D-5L questionnaire.

Exploratory:

- Evaluate dose adaptation and drug-drug interaction (DDI) management strategies.
- Assess potential drug interactions associated with F901318 treatment.

Extended Treatment Exploratory:

- [redacted]
- Evaluate patient-reported outcomes based on the EQ-5D-5L questionnaire.

[redacted]

**Methodology:**

F901318 is the first of the orotomides, a novel class of antifungal agent acting via inhibition of dihydro-orotate dehydrogenase (DHODH). F901318 is active against a wide spectrum of mould and "dimorphic" pathogens but not against yeasts, zygomycetes, and some Fusarium species. This Phase IIb, single-arm, open-label study will evaluate the safety, efficacy and PK profile of F901318 as treatment for infections due to *Lomentospora prolificans*, *Scedosporium* spp, *Aspergillus* spp., and other rare and/or resistant fungi in patients lacking suitable alternative treatment options.

Consenting patients who have either a Proven invasive fungal disease (IFD) due to a fungus known or predicted to be susceptible to F901318 or who have Lower Respiratory Tract Disease (LRTD) with

Probable invasive aspergillosis (IA) will be enrolled in the study and receive treatment with F901318. For patients who have non-LTRD IA (Tracheobronchitis, Sinonasal infection, Central Nervous System infection), only patients with Proven non-LRTD IA can be enrolled.

Patients will be treated until they reach a defined treatment endpoint, up to a maximum of 90 days. Patients should receive treatment for at least 14 days. Patients who are considered by the Investigator to have experienced a successful overall outcome will continue treatment for at least 7 days after resolution of all clinical symptoms and physical signs. Patients judged to have a successful overall outcome on Days 78 to 83 of treatment (and hence requiring 85 to 90 days of total treatment) are eligible to receive up to 90 days of treatment in the main study phase (90 days is the maximum duration of the nonclinical safety toxicology studies). In addition, at the Investigator's request and after discussion with the Medical Monitor (MM), open-label treatment with F901318 may be continued beyond Days 84 to 90 in patients who are judged by the Investigator to need therapy beyond 84 days and who are considered likely to continue to benefit from extended treatment (ET). The Investigator's request to extend treatment with F901318 must be approved by the MM. For patients who are to receive ET with F901318, the End of Treatment (EOT) and End of Study (EOS) for the main study phase are taken as the day on which therapy is completed under the main study phase (Days 1 to 84-90) of this protocol.

The recommended regimen for adults who are not being treated with medications that either inhibit or induce CYP enzymes will be a 1 day oral loading dose regimen of 150 mg F901318 twice daily (bid), dosed 12±1 hours apart, followed by an oral maintenance dose regimen of 90 mg bid, dosed 12±1 hours apart, for Day 2 onwards. Based upon emerging data from both this study and from studies in healthy volunteers, the recommended maintenance dose regimen for oral dosing may be revised to total daily dosages of up to 300 mg divided into two doses. Current guidance will be given by the MM at study initiation and may be updated during study execution.

Efficacy and safety endpoints will be formally assessed at Day 7, Day 14, Day 28, Day 42, Day 84/EOT main study phase and 4 weeks after EOT in the main study phase (4-week follow-up [FU]). Patients are to attend these core study visits, even if treatment has been discontinued before these visits due to a successful outcome. For patients who will receive ET beyond Day 84-90, the Day 84 visit, the EOS visit, and the main study phase EOT visit will be combined into a single Day 84/EOS/EOT visit during the window Day 84-90. An ET-EOT visit will occur on the day that ET dosing stops and will be followed by an ET-EOS follow-up visit that will occur 4 weeks after dosing stops under the ET phase of this protocol.

The efficacy and safety of treatment with F901318 will be assessed [redacted] after the Day 84/Day 90 visit in patients who receive ET, and 4 weeks after the end of ET.

Quality of life will be assessed [redacted]

Patients will either have Proven IFD known or predicted to be susceptible to F901318, or will have Probable LRTD IA. Proven IFD or Probable LRTD IA will be based on the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria.

Patients will initially be assigned by the Investigator to one of the following categories, based on the nature of the IFD:

1. *Lomentospora* (*Scedosporium*) *prolificans* (LoPro),
2. *Scedosporium* spp.,
3. *Aspergillus* spp.,
4. Other F901318-susceptible fungi (as described in the Investigator's brochure [IB])
5. Probable LRTD IA.

Patients with Probable LRTD IA must meet the EORTC/MSG requirements for high risk host factor, clinical features and mycological criteria. Patients with Probable LRTD IA may be re-assigned to the Proven category if the infection is subsequently proven.

Patients will also have limited 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.
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 events (AEs) (e.g., increase in serum creatinine above upper limit of normal [ULN] 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 intravenous (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 polymerase chain reaction (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 in the eCRF.

Once enrolled, patients may remain in the study at the Investigator's discretion if the Investigator judges that the patient is responding to F901318, even if subsequent laboratory data suggest an alternative therapy might be possible. For example, if an isolate of LoPro is found to have unexpectedly low azole minimum inhibitory concentrations (MIC), the patient may remain in the study.

**Pharmacokinetics (PK)**

Sampling for pharmacokinetic (PK) analysis will be performed in all patients. There are 3 categories of PK analysis: Trough, Unscheduled Trough, and Intensive.

Trough PK: All trough samples will be taken within 15 minutes prior to an observed dose of F901318; the dose selected during the day can be at the Investigator's discretion. Trough samples will be taken on Days 10, 14, 21, 28, 42, 56, 70 and Day 84/main study phase EOT (if EOT is before Day 84), and at each visit up to the end of ET for patients who receive ET. These samples will be split and shipped to (a) the regional hub for rapid trough PK analysis and (b) the appropriate central laboratory.

Intensive PK: [redacted] Timing of samples is relative to the oral dose. These samples will be shipped to the appropriate central laboratory.

Unscheduled Trough PK: To permit the analysis of potential DDIs, additional unscheduled samples may be collected as needed in discussion with the MM and PK consultant, where trough samples will be taken within 15 minutes prior to an observed dose. These samples will be split and shipped to (a) the regional hub for rapid trough PK analysis and (b) the appropriate central laboratory.

Analyses: Samples shipped to the regional hub for rapid trough PK analysis (Scheduled and Unscheduled) will be tested for F901318 alone. All PK samples (Trough and Intensive PK, both Scheduled and Unscheduled) will be shipped to the appropriate central laboratory and will be tested for both F901318 and [redacted]

**Rapid PK Analysis**

Regional hubs will be set up by the Sponsor for the rapid analysis of all Trough PK samples for F901318 (both Scheduled and Unscheduled).

[redacted]

| | |
|---|---|
| [redacted]<br>**Independent Data and Safety Monitoring Board (IDSMB)**<br>An IDSMB will conduct periodic reviews of study data (including data for patients receiving ET) to confirm the safety and appropriateness of the treatment dosing regimen.<br>**Data Review Committee (DRC)**<br>Study data will be independently assessed by a DRC. Analysis of data will be based on DRC-adjudicated disease categories, and analysis of efficacy will be based primarily on the DRC-adjudicated outcomes. Data from ET will not be assessed by the DRC.<br>**Study Blinding Procedures**<br>This is an open-label study. | |
| **Planned Number of Patients:** | It is anticipated that total enrolment will be approximately 200 patients. There are no restrictions on the numbers of patients enrolled into the Proven categories with positive identification of the fungal pathogen. [redacted] |
| **Diagnosis and Criteria for Inclusion:** | **General Inclusion Criteria**<br>1) Male and female patients aged ≥ 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<br>OR<br>Patients unable to write and / or read but who fully understand the oral information given by the Investigator (or nominated representative) who have given oral informed consent witnessed in writing by an independent person and in compliance with local regulations.<br>Unconscious patients may not enter the study.<br>2) Ability and willingness to comply with the protocol.<br>3) Patients must be able to take oral medication.<br>4) Female patients must be non-lactating and at no risk of pregnancy for one of the following reasons:<br>a) Postmenopausal for at least 1 year;<br>b) Post-hysterectomy and / or post-bilateral ovariectomy;<br>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 birth control throughout the course of the study period:<br>i) Established use of oral, injected, transdermal, intravaginal or implanted hormonal methods of contraception associated with inhibition of ovulation<br>ii) Placement of an intrauterine device or intrauterine hormone-releasing system<br>iii) Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)<br>iv) Bilateral tubal occlusion<br>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). |

| | |
|---|---|
| | 5) 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.<br>6) Patients with confirmed Proven IFD (based on EORTC/MSG criteria) in the following categories*:<br>a) *Lomentospora* (*Scedosporium*) *prolificans* (LoPro),<br>b) *Scedosporium* spp.,<br>c) *Aspergillus* spp.,<br>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).<br>**OR** with<br>e) Probable LRTD IA who meet the EORTC/MSG requirement for high risk host factor, clinical features and mycological criteria.<br>*Enrolment is based on presumed F901318 susceptibility for categories a-c and selected other species as described in the IB. For IFD due to isolates from species of uncertain susceptibility, enrolment may occur with the approval of the MM before isolate susceptibility is confirmed. If an isolate is not available for shipping to the appropriate central lab for susceptibility testing, susceptibility will be predicted from species identification determined locally. If the isolate is subsequently found to be resistant, study therapy may be continued or discontinued based on clinical response at the discretion of the Investigator. Patients with infections due to multiple fungi can be enrolled provided at least one fungus is known or predicted to be F901318-susceptible AND the patient has limited alternative treatment options for that fungus as defined in Inclusion Criterion 7. As a specific example, a patient with simultaneous IA due to an azole-resistant strain and also invasive mucormycosis could be enrolled and treated with the combination of F901318 and isavuconazole. The choice of additional agents to treat other fungi should also consider the limitations applied to allowed medications. Cases of polyfungal infection should be discussed with the MM.<br>7) Patients will ALSO have limited alternative treatment options based on meeting one or more of the following criteria:<br>a) **Known or predicted resistance of the infecting isolate to all licensed agents**. LoPro automatically meets this criterion.<br>b) **Failure of available therapy.** Failure to improve based on clinical or radiologic grounds despite receiving at least 7 days of standard antifungal treatment AND alternative licensed agents are either predicted to be ineffective or are contraindicated,<br>c) **Intolerance to available therapy.** Current therapy cannot be continued due to therapy-related adverse reactions (e.g., increase in serum creatinine above ULN 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,<br>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,<br>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<br>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 one of the following is true: |

| | |
|---|---|
| | i) Azole-resistance is known based on susceptibility testing of the infecting isolate,<br>ii) Azole-resistance is predicted by PCR or similar molecular diagnostic tool,<br>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),<br>iv) An azole would be acceptable therapy but it is known or predicted that unmanageable DDIs will occur<br>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. |
| **Exclusion Criteria:** | 1) Women who are pregnant or breastfeeding.<br>2) Known history of allergy, hypersensitivity, or any serious reaction to any component of the study drug.<br>3) Patients with chronic aspergillosis, aspergilloma or allergic bronchopulmonary aspergillosis.<br>4) Suspected zygomycosis (mucormycosis) as the IFD used to qualify 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.<br>5) Microbiological findings (e.g., bacterial, virological) or other potential conditions that are temporally related and suggest a different aetiology for the clinical features.<br>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 enrolment, then such patients are eligible for enrolment.<br>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).<br>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.<br>9) Patients previously enrolled in a study with F901318.<br>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.*<br>11) Patients receiving treatment limited to supportive care due to predicted short survival time.<br>12) Patients with a baseline prolongation of QTcF ≥500 msec, or at high risk for QT/QTc prolongation, e.g.<br>a) a family history of long QT syndrome<br>b) other known pro-arrhythmic conditions<br>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:<br>a) Total bilirubin ≥2 x ULN<br>b) Alanine transaminase or aspartate transaminase ≥3 x ULN.<br>c) Patients with known cirrhosis or chronic hepatic failure.<br>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 enrolment.<br>15) Additional exclusion criteria required by local regulatory authorities. |
| **Duration of Treatment:** | Duration of treatment in the main study phase of this study is limited to 90 days and will be at the discretion of the Investigator based on the site and severity of the IFD, the patient's underlying disease, and the rate of clinical response. All patients should receive treatment for at least 14 days.<br>Treatment with F901318 beyond 90 days in an ET phase of the study may be approved by the MM if requested by the Investigator for those patients who are considered likely to continue to benefit from extended treatment. |
| **Test Product, Dose and Mode of Administration:** | F901318 will be provided as an oral formulation.<br>This is a Phase IIb protocol and the dosing regimen for F901318 may be updated during the study. The dosing regimen for adults who are not being treated with medications that either inhibit or induce CYP enzymes will be a 1-day oral loading dose regimen of 150 mg F901318 bid, dosed 12±1 hours apart, followed by a maintenance dose regimen of 90 mg bid, dosed 12±1 hours apart, for Day 2 onwards. As this is the first study in which F901318 has been administered to patients, the target dosing regimen may need to be revised based upon emerging data, to ensure that the majority of patients achieve target plasma levels from the start of treatment. The revision to target doses will be captured in the Dose Guidance Manual. The dosage regimen will be determined from the Dose Guidance Manual (and following discussion with the MM if necessary).<br>• An adjustment to loading and/or maintenance doses of F901318 may be required for patients who are being treated with drugs that either inhibit or induce CYP enzymes (or if such drugs are started or stopped); treatment of these patients must be discussed with the MM.<br>• An adjustment to the maintenance dose of F901318 may be required if patients develop abnormal liver enzymes; treatment of these patients must be discussed with the MM.<br>• Based upon clinical evaluation of efficacy by the Investigator, stepwise increases of maintenance doses of F901318 (to 120 mg bid then 150 mg bid) may be permitted, following discussion with the MM.<br>No dietary restrictions around time of dosing will be applied, although timing of meals or enteral feedings prior to each trough PK sample, and prior to and during Intensive PK sampling will be documented. |
| **Reference Therapy, Dose, and Mode of Administration:** | This is an open-label study and results will be compared with historical data. |
| **Concomitant medication:** | Concomitant administration of teriflunomide and leflunomide is prohibited. There are no other absolutely prohibited or contraindicated medications. However, there are potential DDIs with F901318 and the choice of concomitant medications should take this into consideration. The impact of F901318 upon cytochrome P450 (CYP) 3A4 has been shown to be mild; transplant drugs and other medications which are sensitive CYP3A4 substrates and with potential DDI liability will, where possible, be monitored, and changes in drug treatment will be recorded. Use of concomitant medications that may affect the PK profile of F901318 must be |

| | |
|---|---|
| | discussed and approved by the MM. An extra visit for Unscheduled Trough PK sampling (for rapid PK analysis of F901318) will occur 3 to 5 days after starting or stopping such concomitant medication, to support evaluation of potential DDIs.<br>Concomitant treatment with cytostatic anti-cancer agents (initiation or continuation of treatment) is acceptable, provided assessment of study endpoints is expected to be feasible based on the Investigators clinical judgement, potential impact on adherence to study procedures and endpoints, and the lack of treatment alternatives. Concomitant treatment with cytostatic anti-cancer agents must be discussed with and approved by the MM.<br>Data to date suggest that F901318 does not prolong the QTc interval, and concomitant agents with known potential to prolong the QTc interval may be used with caution. Ongoing therapy with an agent known to have a risk of QT prolongation is not a contraindication for enrolment provided the patient meets the requirements of Exclusion Criterion 12. After enrolment, initiation of new concomitant treatment with known QTc-prolonging agents must be discussed with and approved by the MM. |
| **Concomitant Antifungal Therapy:** | In order to meaningfully analyse the efficacy of F901318, it is important to avoid concomitant use of other systemic antifungal agents with known or potential activity against the primary fungal infection. The constraints on the choice of additional agents may be complex and thus use of any other systemic concomitant antifungal or combination treatment (such as addition of terbinafine for confirmed *Lomentospora prolificans* infections or an echinocandin to manage infection due to *Candida*) is permitted but is discouraged.<br>Antifungal combinations should be based on the Investigator's clinical judgement and must be discussed with the MM.<br>Depending on the treatment given, an extra visit for Unscheduled Trough PK sampling (for rapid PK analysis of F901318) may be required 3 to 5 days after starting or stopping such concomitant medication, to support evaluation of potential DDIs. |

**Criteria for Evaluation:**

Efficacy Endpoints:

Primary Endpoint:

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

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.
- 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.
- 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.
- Quality of life (patient-reported outcome) [redacted], based on the EQ-5D-5L questionnaire.

*Note: For patients who will* 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. Subsequent visits* [redacted] *to assess the safety of continued treatment and to assess the need for further treatment, and there will be a FU visit 4 weeks after ET is completed.*

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.
- [redacted].
- Changes in concurrent medication dose and/or frequency resulting from potential DDIs.
- Overall exposure, individual dose modification, dose intensity.

Pharmacokinetics:

- PK data ($C_{min}$; $C_{max}$, $T_{max}$, $AUC_{0\text{-}tau}$, CL/F and Vz/F).
- Effect of concomitant medication on PK profiles.

**Statistical Methods:**

Sample Size Determination:

This is an open-label study, with no randomization or stratification. There is no upper limit to the enrolment of patients with culture-proven infections. [redacted]. Total enrolment into the study is anticipated to be approximately 200 patients. This will enable patients who have no suitable treatment options for their invasive fungal disease and are ineligible for the Phase III trial to enrol into Study 32 and receive treatment with F901318.

F901318 has been granted Breakthrough Therapy Designation by the FDA based on preliminary clinical evidence that demonstrates F901318 may provide substantial improvement over available therapy. As this designation is intended to expedite the development and review of important products, an initial analysis of data will be performed when 100 patients have completed treatment, to enable the Sponsor to formally consider the possibility that initial approval might be achieved based on the data for the population of patients with limited or no treatment options for life-threatening fungal infections.

[redacted]

Analysis Sets:

The analysis sets to be used in this study are:

- All Patients Enrolled analysis set: all patients who provide written informed consent.
- Safety analysis set (SAF): consists of all patients who receive at least one dose of study drug (or part thereof). The SAF will be used for the analysis of all safety data.
- Intent-to-treat (ITT) population: will consist of all patients who receive at least one dose of study drug.
- Modified ITT (mITT) population: will consist of all patients who receive at least one dose of study drug and who are assigned to a DRC-adjudicated disease category. The mITT population and sub-populations based on DRC-adjudicated disease categories will be used for the analysis of efficacy data.
- Trough PK analysis set (Trough PK set): will include all patients who received at least one dose of study drug and have at least one measured trough F901318 plasma concentration.
- Intensive PK analysis set (Intensive PK set): will consist of a subset of the SAF population who have evaluable [redacted] PK data. Further details on sub-categories (dose level and concomitant medication dependent) will be provided in the modelling analysis plan.

General Statistical Considerations:

Data collected in the main study phase up to Day 84/Day 90 and the subsequent 4-week follow-up visit will be included in the data analyses and presented in the clinical study report (CSR). Data collected during ET will not be included in the data analyses or in the CSR, and will be presented in the report addendum.

Analyses will be made using the overall study population and within the DRC-adjudicated baseline disease categories, and will be descriptive in nature. Data will be presented using appropriate summary statistics. Categorical data will be described using absolute and relative frequencies (n and %). Continuous data will be presented using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum). All variables will be listed in individual patient listings, sorted by DRC-adjudicated baseline disease category and patient number.

Given the various patient sub-groups included in this study data may be summarised in the following groupings:

a) Efficacy for all patients.
b) Efficacy by baseline DRC-adjudicated infection category (the 5 categories of Inclusion Criterion 6).
c) Efficacy by disease location (CNS, bone, lung/sinus, skin/subcutaneous, other, disseminated).
d) Efficacy by underlying condition (haematological malignancy, allogeneic haematopoietic stem cell transplant, solid organ transplant, diabetes, active malignant disease, neutropenia at diagnosis, glucocorticoid use, T-cell immunosuppressant use, renal dysfunction).
e) Efficacy by baseline infection status (no prior therapy; progression or lack of response to prior therapy; partial response to prior therapy but alternative continued therapy is needed; complete clinical response to prior therapy but alternative continued therapy is needed).
f) Efficacy by baseline objective measure of infection activity (objective marker of active disease status such as radiological finding, physical examination finding).

[redacted]. Details on sub-group analyses will be provided in the Statistical Analysis Plan.

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).

In the event that a patient is judged to have active disease that merits treatment but where a baseline objective marker of active infection does not exist, said patient will be evaluated only for safety. Any efficacy data from such patients will be listed only.

All other patients will be evaluated for response.

Efficacy Analyses:

Based on the DRC-adjudicated overall response categorized as Success/Failure a response rate will be calculated based on all patients included in the mITT population. In addition, a 95% confidence interval (CI) for the single binomial proportion will be calculated. This 95% CI will be compared with an estimated historical response rate (and 95% CI) both overall and by DRC-adjudicated disease category.

Secondary efficacy analyses will be presented in a similar manner as described for the primary efficacy analysis.

All-cause mortality will be estimated using the Kaplan-Meier method summarizing median time to death, stratified by DRC-adjudicated disease category.

Patient-reported outcomes as measured by the EQ-5D-5L questionnaire will be summarised as the number of patients with each category of response for each of the 5 quality of life questions. In addition, the overall score will be summarised using the number of patients, mean, standard deviation, minimum, median and maximum values.

Safety Analyses:

Frequency tables will be used to present the safety outcomes including incidences of treatment-emergent AEs (TEAE), SAEs (including deaths), TEAEs leading to death, treatment-emergent AESIs, liver-related TEAEs, TEAEs leading to premature treatment discontinuation, TEAEs leading to premature study withdrawal, TEAEs by relationship and TEAEs by severity.

Change from baseline and incidence of pre-defined treatment-emergent abnormalities in vital signs, clinical laboratory test results and ECG results will be summarised. Graphical presentations will also be used to help describe vital signs, selected laboratory test values and ECG parameters.

Pharmacokinetics:

All PK sample collection times and concentrations will be listed and summarised by visit.

For the Intensive PK set, PK parameters will be listed and summarised.

PK of F901318 will be characterised by nonlinear mixed-effects modelling. From this analysis, the influence of various demographic covariates (e.g., body weight, gender) and other patient-specific factors on F901318 trough levels and drug exposure may be assessed. Intensive PK analysis will be performed on data generated in this study in accordance with a separate modelling data analysis plan and reported outside of the CSR.

# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

# 1.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase |
| $AUC_{0\text{-}tau}$ | Area under the curve over the 12 hour dosing interval |
| BMI | Body mass index |
| CI | Confidence interval |
| CL/F | Clearance (oral administration) |
| $C_{max}$ | Maximum plasma concentration |
| $C_{min}$ | Minimum plasma concentration (taken within 15 minutes prior to next study drug dose) |
| CNS | Central nervous system |
| CRO | Contract research organisation |
| CSR | Clinical study report |
| CT | Computed tomography |
| CTCAE | Common terminology criteria for adverse events |
| CYP | Cytochrome P450 |
| DDI | Drug-drug interaction |
| DHODH | Dihydro-orotate dehydrogenase |
| DRC | Data Review Committee |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| eDC | Electronic data capture |
| EORTC MSG | European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group |
| EOS | End of study |

| | |
|---|---|
| EOT | End of Treatment |
| EQ-5D-5L | The EuroQol Group health-related quality of life questionnaire |
| ET | Extended treatment |
| FDA | Food and Drug Administration |
| FU | Follow-up |
| GCP | Good Clinical Practice |
| GM | Galactomannan |
| h | Hour |
| HAC | Hepatic Advisory Committee |
| HIV | Human immunodeficiency virus |
| HRCT | High resolution computed tomography |
| IA | Invasive aspergillosis |
| IB | Investigator's brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| IDSMB | Independent data and safety monitoring board |
| IEC | Independent Ethics Committee |
| IFD | Invasive fungal disease |
| IRB | Institutional Review Board |
| IS | Invasive scedosporiosis |
| ITT | Intent-to-treat |
| IV | Intravenous |
| LoPro | Lomentospora prolificans |
| LRTD | Lower respiratory tract disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIC | Minimum inhibitory concentration |
| mITT | Modified intent-to-treat |
| MM | Medical monitor |
| MRI | Magnetic resonance imaging |
| PCR | Polymerase chain reaction |
| PK | Pharmacokinetic(s) |
| SAE | Serious adverse event |
| SAF | Safety analysis set |
| SAP | Statistical analysis plan |

| | |
|---|---|
| SOP | Standard operating procedures |
| SUSAR | Suspected unexpected serious adverse reaction |
| TDM | Therapeutic drug monitoring |
| TEAE | Treatment-emergent adverse event |
| $T_{max}$ | Time to maximum plasma concentration |
| ULN | Upper limit of normal |
| Vz/F | Steady state volume of distribution (Oral administration) |
| WBC | White blood cell |

# 2.0 INTRODUCTION

## 2.1 Background Information

### 2.1.1 Unmet need in Invasive Fungal Infections

The presence of fungal elements either as mould or yeast in deep tissues of biopsy or needle aspirates that is confirmed on culture and histo-pathological examination can be described as an invasive fungal disease (IFD) (Ascioglu 2002). Radiological evidence of lesions with culture positive for the presence of fungi also confirms the IFD. Clinical features of IFD are variable, and include febrile illness that continues even after prolonged broad-spectrum chemoprophylaxis. 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 (Xie 2008).

Fungi with the potential to cause invasive infections include yeasts and moulds. Of these, the mould fungi from the genera *Aspergillus* and *Scedosporium* represent particular threats, especially to immunosuppressed individuals.

*Aspergillus* spp. are ubiquitous filamentous fungi found in organic matter and in the environment. *Aspergillus* infection may cause a broad spectrum of disease in the human host, ranging from hypersensitivity reactions to direct invasion of tissue (Denning, 1998). Invasive aspergillosis (IA) is a rapidly progressive, often fatal infection that occurs in patients who are severely immunocompromised. The triazole antifungals (especially voriconazole) are often effective and have emerged as standard of care for IA. However, reports of genetically distinct but hard to identify *Aspergillus* species (so-called cryptic *Aspergillus* species) with intrinsic resistance mechanisms (Lamoth 2016), as well as clinical cases of *Aspergillus fumigatus* infection with mutational resistance, most likely caused by widespread agricultural use of azoles, have raised concern about the limited alternative current treatment options (Garcia-Rubio 2017). This is especially problematic as the triazole antifungals are the only available oral therapies for these fungi. When the triazoles are predicted to be inactive because they have already been used as prophylaxis or prior treatment or when resistance to azoles is proven, patients are limited to prolonged and toxic therapy with an amphotericin B (polyene) preparation (Lamoth 2017).

*Scedosporium* spp. are ubiquitously present in the environment. They cause a wide spectrum of infections in man ranging from classical subcutaneous infections, like mycetoma with spread via the lymphatic system, to disseminated infections with central nervous system involvement. Invasive scedosporiosis (IS) is considerably less frequent than IA, but increasing numbers of cases are reported (Tortorano 2014). *Scedosporium* spp. infections are known for their special neurotropic nature and their high rate of therapeutic failures and relapses. In particular, *Scedosporium* (*Lomentospora*) *prolificans* represents a pan-antifungal-resistant

species with mortality rates of up to 90% in immunocompromised patients (Rodriguez-Tudela 2009, Kelly 2016).

Other "uncommon" moulds which are typically resistant to the azole antifungals and/or polyenes include *Rasamsonia* species as well as *Acremonium*, *Scopulariopsis*, *Microascus*, and *Paecilomyces* species.

Despite advances in diagnostics and therapeutics, the mortality rate in immunocompromised patients with IFD is approximately 50% (Nivoix 2008). Currently marketed antifungal drugs for the treatment of IFD target the fungal cell membrane by inhibiting ergosterol synthesis (the triazoles, such as voriconazole), by inhibiting the synthesis of (1,3)-β-D-glucan (echinocandins, such as caspofungin) or by binding to ergosterol and disrupting membrane integrity (the polyene Amphotericin B [AMB]) (Magill 2008). Each of these 3 classes of treatment has limitations including limited dosage forms, drug-drug interactions (DDI) and significant adverse reactions. The detection of an increasing incidence of azole-resistant Aspergillus spp. (ECDC 2013) is of particular concern since triazoles, including the gold standard treatment voriconazole, have been the agents of choice in life-threatening IA and the only oral agents available. Resistance to the triazoles approaches 30% in some regions (Verweij 2016). Treatment options for IS are even more limited with intrinsic resistance to polyenes and no current agent with reliable activity against *Lomentospora prolificans*, one of the causative agents of IS (Rodriguez-Tudela 2009, Kelly 2016).

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. 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.

### 2.1.2 F901318 has potential to address that unmet need

F901318, also known as 2-(1, 5-dimethyl-3-phenyl-1H-pyrrol-2-yl)-N-{4-[4-(5-fluoro-pyrimidin-2-yl) piperazin-1-yl]-phenyl}-2-oxo-acetamide, is the first of a new class of antifungal agents. F901318 has a novel, well defined mechanism of action, inhibiting a rate limiting enzyme of fungal pyrimidine biosynthesis, DHODH. F901318 potently inhibits fungal DHODH but is a very poor inhibitor of the human enzyme. This differential activity is consistent with the differences in structure between the human and fungal DHODH enzymes.

As discussed in the Nonclinical Pharmacology section of the IB, F901318 is active against a wide range of *Aspergillus* species including those most commonly associated with human infection. Importantly, F901318 is effective against isolates of *A. fumigatus* resistant to other antifungal agents, *Scedosporium* spp. and *Lomentospora prolificans*; the latter is frequently refractory to all available antifungal agents. F901318 is also active against a range of other

filamentous fungi with the notable exception of the zygomycetes. F901318 has no activity against yeasts, zygomycetes, and some Fusarium species.

Within F901318's spectrum of activity is an evolving panel of other "uncommon" moulds which are typically resistant to the azole antifungals and/or polyenes, including *Rasamsonia* species as well as *Acremonium*, *Scopulariopsis*, *Microascus*, and *Paecilomyces* species. Treatment with F901318 may be of benefit in these IFDs, particularly in patients unable to tolerate alternative treatment options.

Sustained exposure to F901318 is lethal to fungi. Vacuolation, cell wall thinning, and cell wall rupture are seen. Loss of cell membrane integrity can be shown by viable dye exclusion studies.

Nonclinical *in vivo* studies, including pharmacological, toxicological and animal models of human invasive fungal infections, have shown F901318 has a good efficacy, safety and tolerability profile with *in vitro* studies showing that it lacks phototoxicity potential. The CYP-based metabolic profile of F901318 and its weak CYP inhibition potential means that DDIs can be predicted and managed. F901318 is active by both oral and IV routes of administration in nonclinical efficacy studies. Fungal burden can be reduced in lung and brain. Extensive nonclinical PK/pharmacodynamic studies of IA (two *in vivo* animal models, multiple strains and species of *Aspergillus*) have defined sustained exposure with a $C_{min}$ of 0.1 to 0.3 µg /mL as the plasma concentration predicted to be effective in the treatment of invasive fungal infections in man. In addition, [redacted] *in vivo* data from a *Coccidioides immitis* brain model showed improvements in animal survival and clearance of infected brain tissue that could not be achieved with a control azole antifungal.

### 2.1.3 Clinical pharmacology: Potentially efficacious and well tolerated exposures can be achieved after oral and IV dosing

The safety profile of F901318 in humans has been characterized in 294 healthy individuals given F901318 by both the oral and the IV route. [redacted]

[redacted]

[redacted]

No embryotoxicity or teratogenicity has been detected in the rat or rabbit. Nonetheless, as a new molecular entity, F901318 should not be given to pregnant women unless the benefit clearly outweighs the risk.

*In vitro* studies have shown that F901318 is a substrate for CYP1A2, CYP2D6, CYP2C19, CYP3A4, CYP2C9, and CYP2C8, with metabolism being more significant for CYPs 3A4, 2C9, and 2C8. F901318 is not an inducer of any CYP enzyme. In man, hepatic metabolism produces a single major metabolite, [redacted], that circulates at concentrations approximately 40% of the concentration of F901318. This metabolite has MICs for *Aspergillus spp*. that are 16- to 32-fold higher than F901318 and hence is considered to contribute little or no meaningful microbiological activity.

The specific combination of fluconazole (CYP3A4 and CYP2C9 inhibitor) and F901318 has been studied in man and exposure to fluconazole has been shown to increase mean $AUC_{0-12}$ and $C_{max}$ of F901318 by 2.0 and 1.7-fold, respectively. *In vitro* and *in vivo* studies have shown that F901318 is a weak inhibitor of CYP3A4; in a clinical study treatment with F901318 resulted in an approximately 1.6-fold elevation of midazolam exposure. F901318 also shows potential for inhibition of the P-gp, BCRP, and BSEP transporters in *in vitro* studies, and whilst the potential for drug interactions is thought to be low, careful monitoring may be needed for sensitive substrates of these transporters which have narrow therapeutic windows.

Based on these findings, caution should be exercised when F901318 is dosed together with any CYP inducer (this may reduce F901318 levels) or inhibitor (this may increase F901318 levels). In addition, F901318 could increase the exposures of compounds metabolized by CYP3A4.

The Investigator is advised to consult with the MM on concomitant medications that either are metabolized by the liver or that influence hepatic metabolism. Concomitant administration of inhibitors of human DHODH (teriflunomide and leflunomide) is prohibited. Co-dosing with moderate or strong CYP3A4 or 2C9 inhibitors will require a dose reduction for F901318 and guidance on dose adjustment must be sought from the MM. It is anticipated that co-dosing with strong CYP inducers (e.g., phenytoin and rifampicin) will significantly reduce F901318 exposures and is discouraged. It is anticipated that co-dosing with immunosuppressive agents

that are sensitive CYP3A4 substrates (e.g., cyclosporine, sirolimus, or tacrolimus) will be possible, [redacted].

## 2.2 Rationale

In nonclinical studies, F901318 exhibits a highly promising antifungal profile which can potentially address the critical treatment requirements for IFD in a changing clinical environment. 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. Based on the nonclinical efficacy profile, F901318 may offer an effective treatment in patients with a diverse selection of fungal infections.

This study will also assess the PK profile of F901318 in a patient population, some of whom will be receiving concomitant medications. All previous F901318 PK and DDI studies have been conducted in healthy volunteers. The results of this study will provide insight into possible differences between the PK profiles of F901318 in healthy volunteers and in patients, and also on potential F901318 DDIs.

This study will be performed in compliance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable regulatory requirements.

## 2.3 Hypothesis

This is a single-arm, open-label, Phase IIb study. The efficacy, safety and tolerability of treatment with F901318 will generally be presented in a descriptive manner. In addition, the response rates will be compared with estimated historical response rates in the respective DRC-adjudicated disease categories. The PK profile of F901318 will be compared with data from previous studies of F901318 in healthy volunteers.

Invasive fungal 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:

1. **Invasive aspergillosis in immunocompromised patients** is a devastating illness with a mortality that approaches 100% without effective therapy (Verweij 1994; Denning 1996; van der Linden 2011; Dixon 2015; Steinmann 2015). Timely treatment of IA with an effective modern drug may reduce mortality to approximately 20% at 6 weeks (Herbrecht 2002; Maertens 2016).

2. **When IA is or becomes resistant to the azole antifungal agents,** mortality rates are high ranging between 50% to 100% (Verweij 2016), mortality rates that approach that for untreated infection. The emergence of resistance threatens the future of the azoles and highlights the urgent need for new and effective antifungal agents.

3. **Invasive scedosporiosis in immunocompromised patients** is a lethal infection. In a review of 162 cases (Rodriguez-Tudela 2009), mortality was 85% in the subset (n=74) with malignancy and 88% in the subset (n=72) with disseminated disease. Eumycetoma, a chronic progressive skin and bone destructive form of IS, is characteristic in the immunocompetent. Therapy requires extensive surgical debridement and even amputation.

4. **Invasive scedosporiosis in healthy hosts** is not as deadly, but nonetheless causes serious, often mutilating infections due to tissue invasive disease following both traumatic inoculation of fungi and near-drowning (Cortez 2008, Tammer 2011, Tortorano 2014). A larger survey from Australia estimated overall 90-day mortality at 30% (Heath 2009).

[redacted]

## 2.4 Risk Assessment

Based on nonclinical studies, [redacted]. There were a few minor changes in haematological and serum clinical chemistry parameters, but none were toxicologically significant or showed histopathology correlates. Histopathological changes at the injection site were also observed after IV dosing in the rat and primate, where the formulation contained HPCD, PVP and PEG.

[redacted] Peripheral venous irritation was observed in subjects receiving vehicle alone as well as in those receiving F901318, and further development of the IV formulation which contains HPCD alone is underway.

[redacted]

[redacted]

[redacted] patients with major hepatic dysfunction are excluded from the study, and liver enzymes and bilirubin (total and direct) will be monitored throughout the study. An algorithm to manage changes in liver enzymes and bilirubin levels provides a consistent approach to patient care [redacted] (Appendix 3).

The impact of F901318 upon CYP3A4 has been shown to be mild; "transplant drugs" and other medications which are sensitive CYP3A4 substrates with potential DDI liability need to be monitored, and changes in drug treatment will be recorded. [redacted]

With these precautions in place, the benefit: risk assessment is believed to be positive for the main study phase of the protocol. For patients going on to receive extended treatment (ET), the decision to continue to ET is based on the Investigator's assessment that the patient has benefited from therapy to date and that ET will offer value and has a favourable benefit-risk for the patient. Further information on findings in the nonclinical studies and clinical studies are presented in the IB.

# 3.0 STUDY OBJECTIVES

## 3.1 Primary Objective

- 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.

## 3.2 Secondary Objectives

The secondary objectives of the study are to:

- 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 patient-reported outcomes based on the EQ-5D-5L questionnaire.

## 3.3 Exploratory Objectives

- Evaluate dose adaptation and drug-drug interaction (DDI) management strategies.
- Assess potential drug interactions associated with F901318 treatment.

## 3.4 Extended Treatment Exploratory Objective

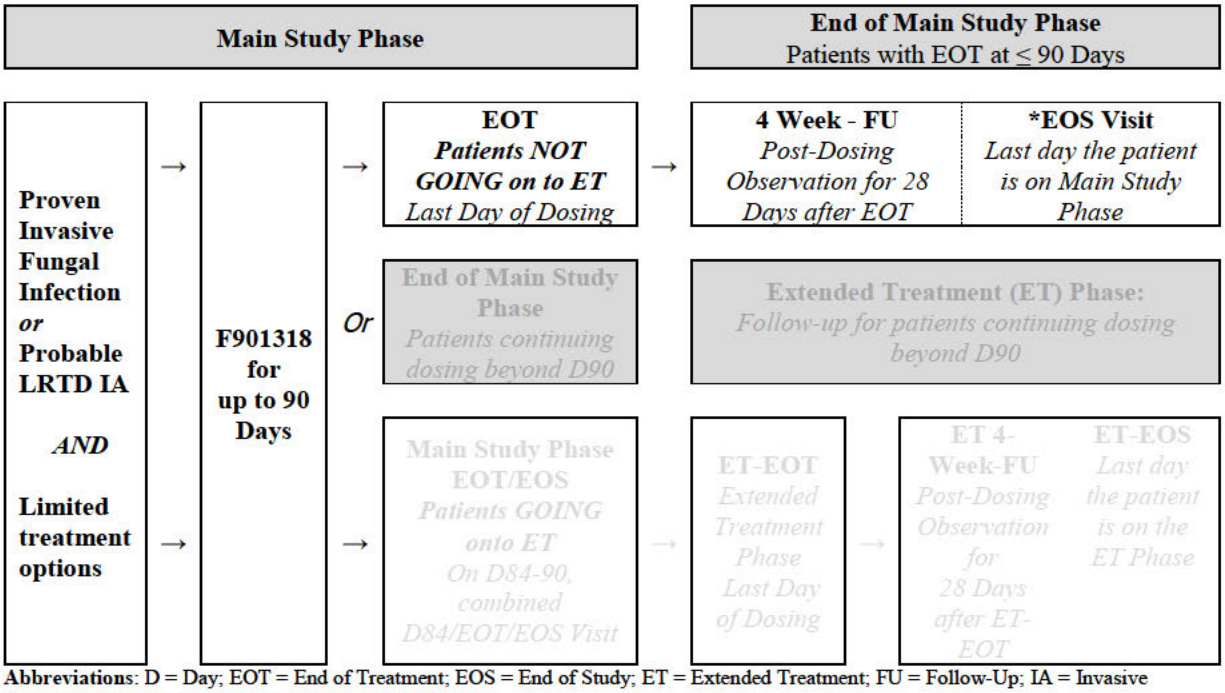
- [redacted]
- Evaluate patient-reported outcomes based on the EQ-5D-5L questionnaire.

# 4.0 INVESTIGATIONAL PLAN

## 4.1 Summary of Study Design

This is an open-label, single-arm, Phase IIb study to evaluate the efficacy, safety, tolerability and PK profile of F901318 in patients with fungal infections lacking suitable alternative treatment options. The study has a 2 phases; the main study phase (Figure 1) and the extended treatment phase (Figure 2).

**Figure 1: Study flow diagram; main study phase**



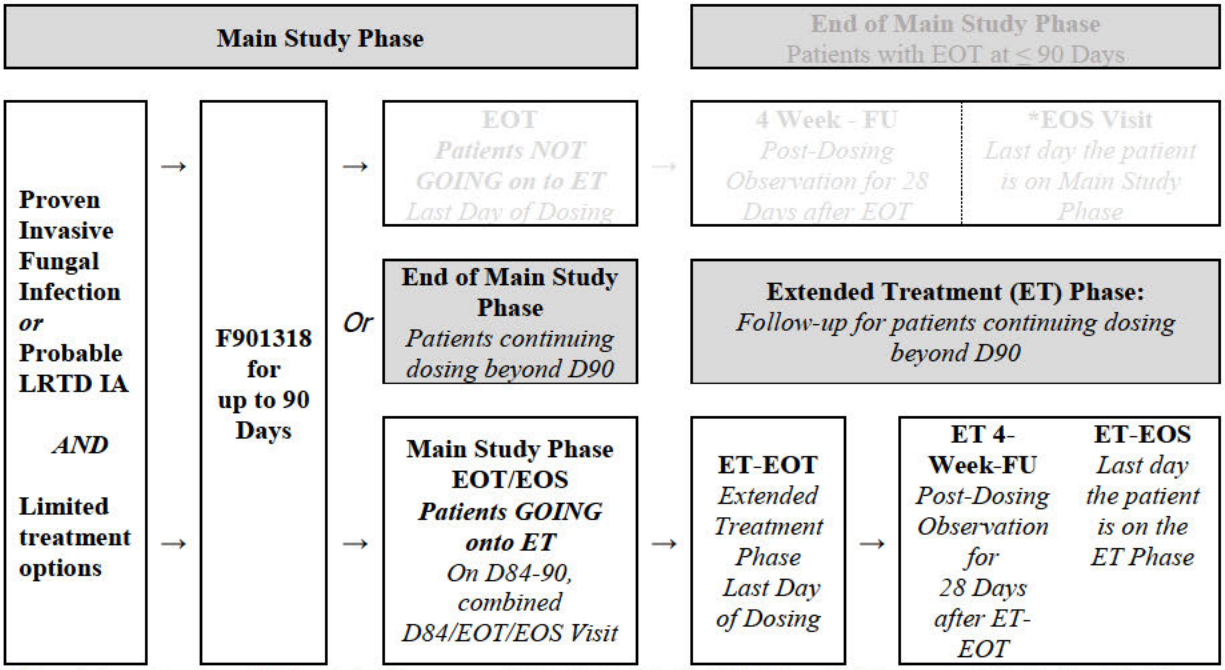

**Abbreviations**: D = Day; EOT = End of Treatment; EOS = End of Study; ET = Extended Treatment; FU = Follow-Up; IA = Invasive Aspergillosis; LRTD = Lower Respiratory Tract Disease

***EOS visit will be the last day the patient is in the Main Study Phase. Note, however, the 4-week FU visit is not necessarily the EOS for all patients as D42 & D84 are required for all patients (successful outcome – assessments, unsuccessful outcome - survival status), accordingly, if treatment is stopped prior to D42/84 the D42 and/or D84 may occur after the 4-week FU visit.***

**Clinical Study Report (CSR) Notes**

1. **The Initial CSR** will be prepared when 100 patients have completed the EOS visit in the Main Study Phase (the first data cut-off date). The Initial CSR will include all data available up to the first data cut-off date, including data for the ET Phase for those patients who have completed the EOS visit in the Main Study Phase and have entered the ET Phase of the study.
2. The **Final CSR** will be prepared at the end of the Main Study, defined as when the last patient has completed the EOS visit in the Main Study Phase. The **Final CSR** will include follow-up for patients through to their Main Study Phase EOS visit. In the **Final CSR,** safety follow-up will include 30 days of follow-up for all events that occur on or before the Main Study Phase EOS visit for each patient. For **patients in the ET Phase**, the CSR will include an additional 30 days of follow-up if there are safety events ongoing at the Main Study Phase EOS visit.
3. [redacted]

**Figure 2: Study flow diagram; extended treatment phase**




Abbreviations: D = Day; EOT = End of Treatment; EOS = End of Study; ET = Extended Treatment; FU = Follow-Up; IA = Invasive Aspergillosis; LRTD = Lower Respiratory Tract Disease.

The rate of enrolment of patients into the study is likely to be low, and it is anticipated that approximately 200 patients will be enrolled at approximately 100 centres globally over at least 60 months. Patients will generally be hospitalised when they are enrolled into the study, but are allowed to leave hospital at any time and continue in the study on an outpatient basis.

Study centres will be selected based on their expertise in diagnosing and managing IFDs. Patients presenting at non-expert centres may be referred to an expert study centre.

Patients will have IFD which can be classified into 1 of 5 disease categories, as described in Inclusion Criterion 6, Section 4.3.1. Four of these categories require Proven IFD. Diagnosis may be based on culture, PCR, or other acceptable methods. For patients with confirmed fungal infection no specific diagnostic method is required. The remaining category refers to patients with Probable LRTD IA, which must meet the EORTC/MSG criteria. All patients with IA must have GM tests completed before enrolment. The initial diagnosis of IFD will be based on the Investigator assessment to minimise any delays in treating patients. Disease categories will subsequently be assessed by an independent DRC. Patients with infections due to multiple fungi can be enrolled provided at least one fungus is known or predicted to be F901318-susceptible.

Consenting patients with a Proven IFD due to a fungus known or predicted to be susceptible to F901318 or with Probable LRTD IA, meeting the inclusion criteria and not meeting any exclusion criteria, will be enrolled in the study. Patients will receive a 1 day loading dose regimen of 150 mg F901318 bid (dosed 12 ± 1 hours apart), followed by a maintenance dose

regimen of 90 mg F901318 bid (dosed 12 ± 1 hour apart) for Day 2 onwards. Based upon Investigator assessment of clinical efficacy, the dose regimen may be increased to 150 mg bid (with stepwise increases from 90 mg bid to 120 mg bid to 150 mg as discussed with the MM). There are no dietary restrictions around the time of dosing, but timing of meals or enteral feedings prior to and during Intensive PK sampling and prior to scheduled or unscheduled trough sampling will be documented.

Patients will be treated until they reach a defined treatment endpoint. All patients should receive treatment for at least 14 days. Patients who are considered by the Investigator to have experienced a successful overall outcome will continue treatment with F901318 for at least 7 days after resolution of all clinical signs and symptoms. The maximum duration of treatment in the main study phase will be 90 days. Patients judged to be a success on Days 78-83 (and hence requiring 85-90 days of total treatment) are eligible to receive up to 90 days of treatment in the main study phase (90 days is the maximum duration of nonclinical safety toxicology studies). In addition, at the Investigator's request and after discussion with the Medical Monitor (MM), open-label treatment with F901318 may be continued beyond Day 90 in patients who are considered likely to continue to benefit from ET. The Investigator's request to extend treatment with F901318 must be approved by the MM. In the case of patients proceeding to the ET phase, the end of treatment (EOT) and end of study (EOS) are taken as the day therapy is completed in the main study phase. Extended treatment may continue as required, but will stop if the study drug becomes commercially available or if development of the study drug is terminated for any reason.

If, at any point during the study period, cultures yield F901318-resistant isolates, patients may remain in the study in the presence of clinical improvement, otherwise they will be considered as treatment failures, treatment with F901318 will be stopped, and the patient will be withdrawn from the study.

To assess efficacy and disease progression during treatment the diagnostic test used to enrol the patient will be repeated. It is essential that the same test is used throughout the study, to provide a robust assessment of change. [redacted]

Assessment of efficacy at other study visits will be in accordance with local practice and as clinically indicated. In patients with IA, GM testing will be conducted more frequently.

Visits and assessments are scheduled as shown in Table 1 for visits up to Day 84/Day 90 and the post-treatment FU in the main study phase, and in Table 3 for ET visits and the post-ET FU in the extended treatment phase.

Safety assessments will be conducted at every study visit, including the ET visits, by recording AEs. Clinical chemistry and haematology assessments, physical examination [redacted], vital signs and ECG will be conducted as shown in Table 1 and in Table 3.

Clinical chemistry and haematology analysis will be conducted by the local laboratory to facilitate patient management, and a second sample will be taken at the same time for analysis by the appropriate central laboratory for visits up to Day 84/Day 90 and the post-treatment FU. All samples taken during ET and at the post-ET FU will be analysed only by the local laboratory.

As an additional safety measure, [redacted] Blood sampling for evaluation of liver function must always be consistent with the Liver Biochemistry Management Algorithm as described in Appendix 3. Analysis of these samples will be conducted by the local laboratory, and a second sample will also be taken for analysis by the appropriate central laboratory for visits up to Day 84/Day 90 and the post-treatment FU.

Trough PK samples will be taken 15 minutes prior to an observed dose on [redacted] For patients proceeding to ET, the Day 84 and main study phase EOT trough PK samples will be combined into a single trough sample at the time of the final visit for the main study phase; thereafter, trough PK samples will be taken at each visit during ET. [redacted]. The schedule of blood sampling for Intensive PK analysis is presented in Table 2. Unscheduled Trough PK samples may be taken, at the request of the Investigator, MM and/or PK Consultant.

The EOS for each patient is defined as the last assessment (scheduled or unscheduled) assigned to the study which that patient completes. For patients receiving ET with F901318, EOS and EOT for the main study phase will be the same visit and occur at approximately Day 90. The EOS overall is defined as the last Day 84/Day 90 visit attended by the last patient in the main study phase of the study (Days 1 to 84-90).

[redacted]

**Table 1 Schedule of Events (Assessments and Procedures): Main Study Phase**

| Period | Screen | Study Treatment | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Day (±window) | -7[a] | 1 | | 3-5 | | 6-8 | 9-11 | 14 ± 2 | 17-18 | 21 ± 2 | 24-25 | 28 ± 2 | 35 ± 2 | 42[b] ± 3 | 49 ± 3 | 56 ± 3 | 70 ± 3 | 84[b] ± 6 | EOT[b,c] ± 3 | Follow-up (4 wks after EOT ± 7d) |
| Study Visit | V1 | V2 | | V4 | | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V12a | V13 | V13a | V14 | V15 | V16 | V17 | V18 |
| General: | | | | | | | | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | | | | | | |

| Period | Screen | Study Treatment | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Day (±window) | -7[a] | 1 | | 3-5 | | 6-8 | 9-11 | 14 ± 2 | 17-18 | 21 ± 2 | 24-25 | 28 ± 2 | 35 ± 2 | 42[b] ± 3 | 49 ± 3 | 56 ± 3 | 70 ± 3 | 84[b] ± 6 | EOT[b,c] ± 3 | Follow-up (4 wks after EOT ± 7d) |
| Study Visit | V1 | V2 | | V4 | | V6 | V7 | V8 | V9 | V10 | V11 | V12 | V12a | V13 | V13a | V14 | V15 | V16 | V17 | V18 |
| [redacted] | | | | | | | | | | | | | | | | | | | | |

a. Screening assessments are to be completed within the 7 days prior to start of treatment unless otherwise specified.
b. To be completed even if treatment was completed prior to these visits due to a successful outcome. Main study phase EOT, Day 42 and Day 84 assessments are required for all patients. FU assessments are required for all patients who do not continue therapy beyond Day 90. Patients with a successful overall outcome are required to return for all

four visits. Patients withdrawn from study drug or with an unsuccessful overall outcome are required to return for the main study phase EOT visit and FU visit but will not be asked to return for the Day 42 and Day 84 visits; however, survival status will be obtained at these timepoints.

c. If the main study phase EOT occurs within 1 week of a scheduled visit, the assessments completed at that visit do not need to be repeated; however, the Investigator must ensure that all assessments required for main study phase EOT have been completed. As an example, Day 84 and main study phase EOT would be the same for a patient who completes 12 weeks of therapy and stops drug. For patients who will 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 Subsequent visits will be every 4 weeks to assess the safety of continued treatment and to assess the need for further treatment, and there will be a FU visit 4 weeks after ET is completed.
d. Only for women of childbearing potential. At screening and on the visits indicated in the schedule of event, only if patient is not hospitalized.
e. During 6 months prior to treatment start. If the qualifying infection was diagnosed before baseline, data regarding the prior symptoms and prior evaluation(s) of the invasive fungal infection should be noted here.
f. All major illnesses or medical history should be captured with particular attention to the 3 months prior to treatment start.
g. Enrolment may occur up to and including Day 1, prior to first dosing
h. Prior and concomitant medication to be reported during 4 weeks prior to treatment start and up to the 4-week FU visit; for chemotherapy a summary of regimens during 12 weeks prior to treatment start should be provided. For T-cell immunosuppressive medications (e.g. cyclosporine, tacrolimus, monoclonal antibodies or nucleoside analogues) given within 90 days prior to screening or any dosing prior to study entry that support the host factor criteria "Treatment with other recognized T-cell immunosuppressants" at the time of the initial diagnosis of the fungal infection.. All other medications given within 4 weeks prior to screening or any dosing prior to study entry that support the host factor criteria "Prolonged use of Corticosteroids". All medications taken during the treatment period. All medications taken during the 4-week post-treatment period.
i. All non-medication procedures (e.g. radiation therapy, blood transfusions, dialysis) including all treatment for IFD (e.g. surgery) associated with the patient's underlying disease received within 2 weeks prior to the first dose of study drug, during the treatment period or during the 4 weeks post-treatment period follow-up period will be recorded in the appropriate section of the eCRF.
j. Reason for hospitalization, date of admission and discharge and type(s) of ward, must be recorded in the eCRF.
k. Diagnostic assessments include mycological culture, histology/cytology, GM, PCR and radiology tests used to confirm enrolment of the patient. It is essential that the same methods are used for both diagnosis and assessment of overall response. Screening assessments and assessments that support the EORTC criteria at the time of the initial diagnosis of the study-qualifying infection (time of the original IFD diagnosis or probable IA assessment) should be reported.
l. As clinically indicated.
m. Baseline (if available) and different (species level) isolates identified during the study will be stored and shipped to the appropriate central laboratory for species identification and susceptibility testing. If infection is due to multiple fungi, isolates for all infecting species should be shipped.
n. Serum GM must be assessed for all patients with proven or probable IA. Serum GM assessments meeting the protocol defined requirements within 10 days prior to first dose of study drug are acceptable for enrolment requirements.
o. Radiological assessment should be performed in accordance with local practice and as clinically indicated. Radiological examination of the site of IFD should utilize the same x-ray/CT/HRCT/or MRI modality as the baseline radiologic examination.
p. If used as part of the enrolment criteria, radiology studies should be repeated at these time points.
q. Bronchoscopic assessment should be performed in accordance with local practice and as clinically indicated.
r. Within 4 weeks prior to screening. See also Section 6.4.2.2: neutropenia is defined as ANC < $0.5 \times 10^9$/L [< 500/mm$^3$]. Neutropenia status will be recorded from the screening visit throughout the 4-week post treatment period. Neutropenic episodes supporting the Host Factor criteria of "Neutropenia" at the time of the initial diagnosis of the invasive fungal infection should also be reported. Absolute neutrophil count results from 4 weeks prior to screening through the patient's last study visit and any values supporting the Host Factor Criteria Neutropenia. Local Laboratory ANCs for all neutropenic episodes (defined as ANC < $0.5 \times 10^9$/L [< 500/mm$^3$]) from 4 weeks prior to screening up to the end of study and those that support a Host Factor Criteria of Neutropenia at the time of the initial diagnosis (which may be greater than 4 weeks prior to Screening). ANC results to cover the period from onset up to and inclusive of the first 2 consecutive ANC values > $0.5 \times 10^9$/L on consecutive days confirming resolution of the episode. When differentials are not performed due to insufficient WBCs, the total WBC count for the day should be recorded.
s. The Screening EQ-5D-5L questionnaire provides the baseline, and should be completed as close to the day prior to the start of treatment as is feasible.
t. Only in patients with abnormalities observed at main study phase EOT.

u. See Table 7 and Appendix 3 for minimum list of tests to perform. Additional samples at unscheduled visits should also be taken if ALT/AST or bilirubin elevations occur (see Appendix 3). [redacted] Blood sampling for evaluation of liver function must always be consistent with the Liver Biochemistry Management Algorithm as described in Appendix 3.

v. Systolic blood pressure, diastolic blood pressure, pulse rate and body temperature; body temperature should be measured via the same route throughout the study period. Vital signs should be measured before study drug administration.

w. ECG on treatment should be performed between 30 min and 4 hours after dosing.

x. [redacted]

y. For patients on sensitive (for example transplant drugs) and moderately sensitive substrates (see Section 5.9.1.5), take a blood sample to measure the level of the substrate prior to starting treatment with F901318 and thereafter based on Investigator's judgement. Results of TDM done up to 7 days prior to commencing treatment are acceptable and a baseline sample need not be taken in such cases.

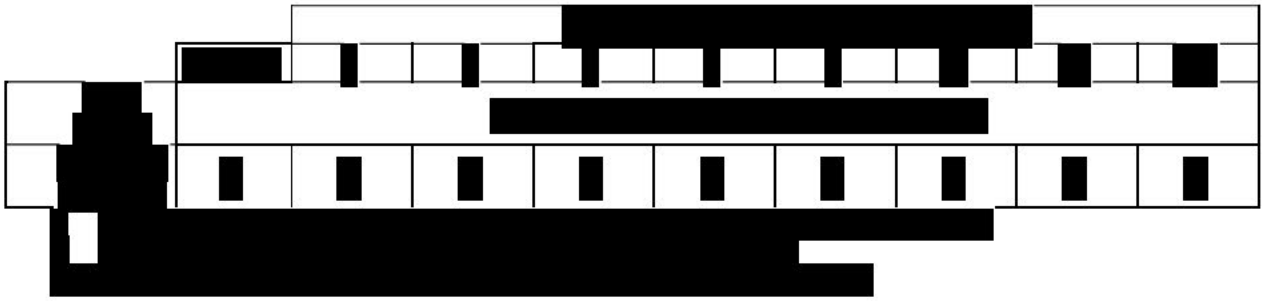
z. Trough F901318 samples should be taken within 15 minutes prior to observed dose, but no earlier than 1 hour prior; the dose selected can be at the Investigator discretion. Unscheduled Trough F901318 levels should also be taken pre-dose 3 to 5 days after starting/stopping concomitant medications which may impact F901318 PK. Time of last meal prior to trough sample must be recorded.

aa. Intensive PK day can take place [redacted] Time of last meal prior to observed dose and during Intensive PK sampling must be recorded.

bb. [redacted]

Assessments in parentheses (X) are to be done in accordance with local practice and the Investigator's clinical judgement.
Abbreviations: AE = adverse event; BT = body temperature; D = Day; ECG = electrocardiogram; EOT = end of treatment; GM = galactomannan; PCR = polymerase chain reaction; PK = pharmacokinetics.

**Table 2** [redacted]



### 4.1.1 Extended Treatment

For patients receiving ET with F901318, visits should be arranged at least once every 4 weeks after the main study phase concludes in the window Day 84-90. Treatment in the ET phase should start on the day following the last treatment day on the main study phase. At each visit, the Investigator should assess the IFD status of the patient. Treatment may be continued if, in the Investigator's opinion, the patient would continue to benefit from further treatment with F901318. At each visit after starting ET, the Investigator must complete the following assessments as described in the Schedule of Events (Table 3) and record the results of the assessments in the eCRF:

- Investigator's assessment of IFD response (as clinically indicated and in accordance with the diagnostic procedures used to identify the IFD)
- Clinical signs and symptoms
- Radiology and/or mycology as clinically indicated and in accordance with local practice
- AE, SAE, AESI, and death (to be documented and reported in accordance with Section 6.4.1)
- Pregnancy and pregnancy test (as appropriate; to be documented and reported in accordance with Section 6.4.1.4)
- Laboratory tests for clinical chemistry and haematology in accordance with Table 7. Increased liver enzymes and bilirubin are to be managed in accordance with Appendix 3. The local laboratory is to be used and analysis at a central laboratory is not required.
- Trough PK sample; regional hub analysis
- Concomitant medication
- Antifungal medication
- Drug accountability
- ECG only if clinically indicated

- [redacted]

After each visit, the Investigator must inform the MM of the patient status, the decision taken to continue treatment or not, and the reasons for the decision.

**Table 3 Schedule of Events: Extended Treatment (Assessments and Procedures)**

| Period | Start of Extended Treatment | Extended Treatment | End of Extended Treatment | Follow-up |
|---|---|---|---|---|
| Study Day (±window) | Main Study Phase Day 85-91[a] | Every 4 weeks ± 7 days | | 4 weeks after End of Extended Treatment ± 7 days |
| [redacted] | | | | |

a) The start of ET visit can be the same as the main study phase EOT/EOS visit at Day 84-90, but no later than Day 91. The first day of ET phase dosing will be the day after the last day of dosing in the main study phase.
b) Only for women of childbearing potential, and only if patient is not hospitalized.
c) Reason for hospitalization, date of admission and discharge and type(s) of ward, must be recorded in the eCRF.
d) Diagnostic assessments include mycological culture, histology/cytology, GM, PCR and radiology tests used to confirm enrolment of the patient. It is essential that the same methods are used for both diagnosis and assessment of overall response.
e) As clinically indicated.
f) Serum GM must be assessed for all patients with proven or probable IA. Serum GM assessments meeting the protocol defined requirements within 10 days prior to first dose of study drug are acceptable for enrolment requirements.

g) If used as part of the enrolment criteria, radiology studies should be repeated at these time points. Radiological assessment should be performed in accordance with local practice and as clinically indicated. Radiological examination of the site of IFD should utilize the same x-ray/CT/HRCT/or MRI modality as the baseline radiologic examination.
h) Bronchoscopic assessment should be performed in accordance with local practice and as clinically indicated.
i) Neutropenia is defined as ANC $< 0.5 \times 10^9$/L [$< 500/mm^3$].
j) Additional samples at unscheduled visits should also be taken if ALT/AST or bilirubin elevations occur (see Appendix 3).
k) Only in patients with abnormalities observed at ET-EOT
l) Only if associated with an AE.
m) [redacted]
n) Trough F901318 samples should be taken within 15 minutes prior to observed dose, but no earlier than 1 hour prior.
Abbreviations: AE = adverse event; ANC = absolute neutrophil count; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; ET = extended treatment; GM = galactomannan; PCR = polymerase chain reaction.

## 4.2 Discussion of Study Design

The overall objectives of this study are to evaluate the efficacy, safety and tolerability of F901318 in the treatment of IFD in patients with no alternative treatment option. These patients will have IFD which meets the inclusion criteria and is predicted to be susceptible to F901318. The diagnostic methods used to identify these patients and to confirm eligibility for the study will vary, and the methods used to assess efficacy or disease progression during treatment will also vary. To manage this variation, the Investigator is required to use the same diagnostic methods for each patient throughout the duration of the study to facilitate the assessment of disease progression. The study is designed to allow flexibility in the process used to identify patients, to facilitate clinical management of patients in accordance with local best practice, and at the same time to provide consistency in the collection of data.

Assessment of efficacy after 42 days and 84 days of treatment has been used in other studies in patients with IFD. Inclusion of these 2 timepoints for assessment of efficacy will support comparison of the data from this study with historical and contemporary clinical data and case reports.

In addition, very lengthy treatment (many months) is sometimes beneficial in treating IFD. [redacted], the main phase of this protocol is limited to 90 days of treatment. However, discussions with study Investigators make it clear that extended treatment is justified for those patients who have benefited from treatment with F901318 but whose IFD has not completely resolved after 84 to 90 days of treatment and who would continue to benefit from further treatment with F901318. No alternative treatment options are available for these patients, and stopping treatment with F901318 after 84 to 90 days could entail a risk of IFD exacerbation. [redacted]

[redacted]

Enrolment of patients into the study is expected to be slow, and there is no basis on which to predict the numbers of patients likely to be enrolled in each category. There is no limit to the enrolment of patients in the categories which require a positive identification of the fungal pathogen. This should allow unrestricted enrolment of patients in these categories. The number of patients with unconfirmed infection (Probable LRTD IA) will be monitored, and enrolment into this category may be stopped at any time by the Sponsor. This approach should facilitate the enrolment of patients with confirmed IFD and also limit the risk of inappropriate treatment in patients who do not have confirmed infection.

This is a single-arm, open-label, Phase IIb study. There is no suitable alternative treatment for patients in this study, and inclusion of a comparator treatment arm would not be appropriate. In addition, it is unlikely that any single comparator would be appropriate for all disease categories.

In clinical PK studies, the terminal half-life of F901318 is 24 to 30 hours. The use of a loading dose regimen of 150 mg bid (given at 12 ± 1 h intervals) to initiate treatment will allow a therapeutically effective blood concentration to be achieved rapidly. The daily maintenance dose of 90 mg bid (given at 12 ± 1 h intervals) has been selected to provide sustained exposure to blood concentrations of F901318 predicted to be clinically effective. However, should ongoing studies in healthy volunteers demonstrate that an alternative dosing regimen (up to three times daily dosing of a total daily dose of up to 300 mg) provides blood levels that fall within the target therapeutic range, a revised regimen may be adopted.

Safety of patients will be monitored throughout the study. [redacted]

Enrolment of patients into this study will be based on the Investigator's assessment of the IFD, and the likely susceptibility of the infection to treatment with F901318. The Sponsor will provide a comprehensive summary of the range of fungal species which have been tested for susceptibility to F901318, and will update this summary as new information becomes available. In addition, the MM will be available to provide advice to the Investigator.

## 4.3 Selection of Study Population

### 4.3.1 Inclusion Criteria for Main Study Phase

Patients may be entered in the study only if they meet all of the following 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 (or nominated representative) who have given oral informed consent witnessed in writing by an independent person and in compliance with local regulations. Unconscious patients may not enter the study.
2. Ability and willingness to comply with the protocol.
3. Patients must be able to take oral medication
4. Female patients must be non-lactating and at no risk of pregnancy for one of the following reasons:
   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 birth control 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).
5. 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.

6. Patients with one of these 4 forms of Proven invasive fungal infection* confirmed by culture or other diagnostic based on EORTC/MSG criteria (see Appendix 2) and 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.

   *Enrolment is based on presumed F901318 susceptibility for categories a-c and selected other species as described in the IB. For IFD due to isolates from species of uncertain susceptibility, enrolment may occur with the approval of the MM before isolate susceptibility is confirmed. If an isolate is not available for shipping to the appropriate central lab for susceptibility testing, susceptibility will be predicted from species identification determined locally. If the isolate is subsequently found to be resistant, study therapy may be continued or discontinued based on clinical response at the discretion of the Investigator. Patients with infections due to multiple fungi can be enrolled provided at least one fungus is known or predicted to be F901318-susceptible AND the patient has limited alternative treatment options for that fungus as defined in Inclusion Criterion 7. As a specific example, a patient with simultaneous IA due to an azole-resistant strain and also invasive mucormycosis could be enrolled and treated with the combination of F901318 and isavuconazole. The choice of additional agents to treat other fungi should also consider the limitations applied to allowed medications (Section 5.9.2). Cases of polyfungal infection should be discussed with the MM.

7. 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.

#### 4.3.1.1 *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.

### 4.3.2 Exclusion Criteria for Main Study Phase

Patients will not be entered in the study for any of the following reasons:

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 qualify 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 aetiology 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 enrolment, then such patients are eligible for enrolment.

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. Unless approved by the MM, 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 enrolment (Section 5.9.1).

15. Additional exclusion criteria required by local regulatory authorities. These include, but are not limited to,:

    - Patients accommodated in an institution because of regulatory or legal order.
    - Prisoners or patients 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 situation during study implementation/course that may raise ethics consideration.

#### 4.3.2.1 *Exclusion Criteria for Extended Treatment Phase*

1. Patients who are not suitable for 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.

2. Patients who are unwilling or unable to continue the contraceptive measures as described for the main study phase.

### 4.3.3 Patient Restrictions

The following restrictions may affect patient participation in this study:

- Concomitant medication prohibitions and restrictions as described in Section 5.9.
- Female patients of childbearing potential must take adequate contraceptive precautions before starting study drug treatment, for the entire duration of the study and until at least 30 days after the last dose of study drug. Adequate contraceptive precautions include the following:
  - Established use of oral, injected, transdermal, intravaginal or implanted hormonal methods of contraception associated with inhibition of ovulation
  - Placement of an intrauterine device or intrauterine hormone-releasing system
  - Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
  - Bilateral tubal occlusion
  - 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).
- 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 the last dose of study drug.
- No dietary restrictions around time of dosing will be applied, although timing of meals or enteral feedings prior to and during Intensive PK sampling will be documented.

### 4.3.4 Patient Withdrawal

All patients are free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The criteria for enrolment are to be followed explicitly. If a patient who does not meet enrolment criteria is inadvertently enrolled, that patient should be withdrawn from the study and the Sponsor or Sponsor's designee must be contacted. An exception may be granted in rare circumstances where there is a compelling safety reason to allow the patient to continue. In these rare cases, the Investigator must obtain documented approval from the Sponsor or Sponsor's designee to allow the patient to continue in the study.

In addition, patients will be withdrawn from study drug and from the study in the following circumstances:

- The Investigator decides that the patient should be withdrawn.
- Intolerable AE; the study drug is to be discontinued and appropriate measures are to be taken. The Sponsor or Sponsor designee must be notified immediately.

- Clinically significant laboratory value; depending on the observed value, the study drug may need to be discontinued. Prompt consultation with the MM is required.
- ALT or AST meet criteria for major enzyme elevation AND total bilirubin > 1.5x ULN (if baseline < ULN) OR > 1.5x baseline (if baseline > ULN) without evidence of obstruction, malignancy, impaired glucuronidation capacity or another explanation as detailed in Appendix 3. Study drug must be stopped, and patient follow-up must be conducted in accordance with Appendix 3.
- The patient is unwilling to continue in the study (withdrawal of consent).
- Lack of efficacy.
- Lack of compliance with protocol.
- The Sponsor, for any reason, terminates or suspends the study (see also Section 4.3.5).
- Cultures performed during the treatment period yield F901318-resistant isolates judged clinically relevant and there is no clinical improvement in the opinion of the Investigator (considered as treatment failure).

Patients who discontinue the study early will have early termination procedures performed in accordance with the main study phase EOT visit as shown in the Schedule of Events.

Patients who are withdrawn from the study will not be replaced.

The post-treatment follow-up visit (4 weeks after main study phase EOT) should be performed for all patients who receive at least one dose of study drug, wherever possible, except for patients who receive ET beyond Day 90. A post-treatment follow-up safety visit 4 weeks after the last dose of study drug should be performed for all patients who receive ET, but this is not considered to be the main study phase EOS or EOT visit.

The reason for discontinuation of study drug and withdrawal from the study will be recorded in the eCRF.

Patients who sign informed consent and are assigned a patient ID but do not meet the eligibility criteria will be considered Screen Failures. If the Investigator believes rescreening is warranted, a patient can be rescreened. There is no limit to the frequency or number of times a patient may be rescreened. Refer to the Schedule of Events for the list of procedures required at Screening.

### 4.3.5 Study Termination

During the course of the study, it is possible that new risks or toxicities related to F901318 will be identified from this study or from other clinical or nonclinical studies conducted in parallel. If these result in a significant negative change in the benefit-risk, the clinical study may be put on hold or terminated. In addition, external medical and/or ethical insights could have an effect on

clinical study progress. Further, the study could be interrupted or terminated based on a decision by the Sponsor, based on a decision by a responsible authority, upon withdrawal of approval by the ethics committee, or upon advice from the IDSMB or the Hepatic Advisory Committee (HAC). The clinical study can also be stopped if enrolment is deemed adequate by the Sponsor.

# 5.0 STUDY TREATMENTS

## 5.1 Treatments Administered

The investigational product in this study is F901318 (olorofim). This is an open-label study in which F901318 is given to eligible patients for up to 90 days during the main study phase (see Figure 1). Open-label treatment with F901318 may be continued beyond Day 90 in patients who are considered likely to continue to benefit from ET with F901318 (see Figure 2).

[redacted] dosing regimen for adults has been simplified to 150 mg bid (dosed at 12 ± 1 h intervals) followed by a maintenance dose regimen of 90 mg bid (dosed at 12 ± 1 h intervals) for Day 2 onwards. Nonetheless, and as this is the first time F901318 has been administered to patients, the target oral dosing regimen may yet need to be revised based upon emerging data, to ensure that the majority of patients achieve target plasma levels from the start of treatment. Any such revision to target doses will be captured in the Dose Guidance Manual.

The maximum total daily dose of F901318 is 300 mg, given as 2 doses (dosed at 12 ± 1 h intervals). Detail of the dosing regimen (number of tablets to be administered and the frequency of administration) will be provided in the Dose Guidance Manual. The recommended maintenance dose regimen may change during the study and current guidance should be confirmed with the MM at study initiation.

An adjustment to loading and/or maintenance doses of F901318 may be required for patients who are being treated with drugs that either inhibit or induce CYP enzymes (or if such drugs are started or stopped); treatment of these patients must be discussed with the MM. An adjustment to the maintenance dose of F901318 may be required if patients develop increased liver enzymes and/or bilirubins (See Appendix 3); treatment of these patients must be discussed with the MM. Adjustment to the maintence dose may also be required if trough plasma levels of F901318 are outside the target range (as defined in the Dose Guidance Manual); treatment of these patients must be discussed with the MM.

Adjustment to the dose may be required if an Investigator considers the clinical response to be sub-optimal, where after discussion with the MM, dose increments may be implemented as follows:

1. [redacted]

[redacted] Blood sampling for evaluation of liver function must always be consistent with the Liver Biochemistry Management Algorithm as described in Appendix 3.

Dose Interruptions

Dosing interruptions are to be avoided but may be necessitated by patient care circumstances.

- The reason for dosing interruption should be documented.
- The approach to pausing and restarting dosing should follow the general dosing guidelines.
- If the interval between the last pre-interruption dose and the first post-interruption dose exceeds 48 hours, redosing should begin with a loading dose regimen.
- Guidance from the MM should be obtained.

Patients will be treated until they reach a defined treatment endpoint, up to a maximum of 90 days in the main study phase. Patients who are considered by the Investigator to have experienced a successful overall outcome will continue treatment for at least 7 days after resolution of all clinical symptoms and physical signs. All patients must receive at least 14 days of treatment, unless treatment is stopped due to one of the withdrawal criteria described in Section 4.3.4. Patients judged to be a success on Days 78-83 (and hence requiring 85-90 days of total treatment) are eligible to receive up to 90 days of treatment in the main study phase (90 days is the maximum duration of nonclinical safety toxicology studies); in addition, at the Investigator's request and after discussion with the MM, open-label treatment with F901318 may be continued beyond Day 90 in patients who are considered by the Investigator to be likely to continue to benefit from ET. The Investigator's request to extend treatment with F901318 must be discussed with the MM and approved by the MM. In the case of patients proceeding to the ET phase, EOT and EOS for the main study phase are defined as the day therapy is completed in the main study phase at approximately Day 90.

Once enrolled, patients may remain in the study at the Investigator's discretion based on the site and severity of the IFD, the patient's underlying disease and the rate of clinical response, even if subsequent laboratory data suggest an alternative therapy might be possible. For example, if an isolate of LoPro is found to have unexpectedly low azole MICs, the patient may remain in the study.

For all patients except those receiving ET, the Follow-up Visit will take place 4 weeks (±7 days) after the last administration of study drug, and may occur before or after Day 42 and/or Day 84 (i.e., it is not necessarily the "end of study" visit for a given patient). For those patients receiving extended F901318 treatment, the main study phase EOS and EOT will be the same visit and will

occur at approximately Day 90, and, the follow-up safety visit will take place 4 weeks (±7 days) after the last administration of study drug.

Patients with a successful overall outcome at the main study phase EOT, who subsequently require further treatment with F901318 before the 28-day post-treatment Follow-up Visit, may receive further treatment with F901318 following consultation with the MM. In this situation, stopping treatment with F901318 then resuming treatment will be considered to be a treatment interruption, and if the interval is more than 48 hours redosing should begin with a loading dose regimen. In addition, appropriate diagnostic tests should be undertaken to determine the cause of the change in clinical status and the susceptibility to F901318 of any identified IFD.

Patients with a successful overall outcome at the main study phase EOT prior to Day 42 must return for Day 42 and Day 84 Visits, even if they are no longer under study treatment. If the administration of systemic antifungals as prophylaxis is anticipated, patients should stay on study treatment through Day 42.

Patients with an unsuccessful overall outcome at the main study phase EOT and requiring alternative systemic antifungal therapy will not be asked to return for Day 42 and/or Day 84 Visits; however the survival status at these timepoints will be collected at a minimum.

## 5.2 Identity of Investigational Products

Details of the F901318 dosage form used in this study are provided in Table 4.

**Table 4 Investigational Products**

| Investigational product | Formulation | Dosage form and strength | Manufacturer |
|---|---|---|---|
| F901318 | Oral tablet | 30 mg per tablet | [redacted] |

F901318

The oral formulation used in this study is a tablet containing 30 mg F901318 and standard pharmacopoeial excipients; [redacted]

The oral product should be stored and transported refrigerated (2-8°C).

[redacted]

## 5.3 Packaging and Labelling

The F901318 tablet will be packed into 64 count, 50 mL high density polyethylene bottles, with polypropylene twist off caps containing desiccant. Each bottle will have an approved clinical study label that complies with local regulations.

## 5.4 Method of Assigning Patients to Treatment Group

This is a single-arm, open-label, Phase IIb study. Patients who have provided informed consent, met all inclusion criteria and not met any exclusion criteria will receive treatment with F901318. The study centre will request the study drug assignment using the Interactive Web Response System (IWRS).

All patients will be managed by IWRS. The study centre will contact IWRS and patients will be assigned their 8-digit patient number by the IWRS at the time of enrolment. The IWRS will provide the medication kit/bottle number(s) of the study drug to be dispensed.

## 5.5 Selection of Doses in the Study

Based on data from clinical pharmacology PK studies, preliminary PK data from the ongoing study and Population PK modelling predictions, the dose of F901318 selected for this study is predicted to provide sustained and stable exposure to systemic concentrations of F901318 within the range expected to be effective against the target pathogens [redacted]

## 5.6 Selection and Timing of Dose for Each Patient

The recommended regimen will be as described in Section 5.1. The recommended regimen may change during the study and current guidance should be confirmed with the MM at study initiation.

There are no dietary restrictions associated with timing of F901318 dosing. If the patient vomits after taking oral F901318, the patient should not repeat the dose but should wait until the next dose as scheduled. Any patient who vomits twice in 1 day should inform the Investigator.

The time at which each dose is taken will be recorded in a patient dosing diary. The diary must be completed for hospitalized patients as well as for outpatients.

## 5.7 Trough PK Sample Analysis

Therapeutic drug monitoring for F901318 with dose adaptations to maintain optimal trough levels within a pre-specified target range will no longer be used. Rapid analysis of trough levels of F901318 will remain to monitor the potential impact of concomitant medication upon F901318, to have access to systemic exposure [redacted] and to support ongoing analysis of the safety profile of F901318 across the population.

The Sponsor is responsible for setting up regional hubs for rapid trough PK analysis, each of which will have access to a suitably validated F901318 assay. Sample collection to receipt at the regional hub will ideally take no more than 1 working day, with analysis being completed within 1 working day of sample receipt (i.e. 2 working days turnaround time between sample collection and trough PK data availability).

Guidance for dose adjustment (for use by the MM and PK consultant) will be available prior to study start and will accommodate dosing regimen changes due to concomitant medication, clinical judgement in response or when elevations in liver function tests occur which meet or exceed the threshold defined as moderate in Appendix 3 of the protocol. Should any dose adaptations be required, the MM and/or PK consultant will advise of any additional Unscheduled Trough PK sampling requirements, to enable the impact of the dose adaptation to be assessed.

## 5.8 Blinding

This is an open-label study. Study data reviewed by the DRC and Independent Data and Safety Monitoring Board (IDSMB) will not be blinded.

## 5.9 Prior and Concomitant Treatments

Prior medications associated with the initial management of the study-qualifying fungal pathogen will be recorded in the eCRF. All other anti-fungal medication taken during the 6 months prior to study screening will be recorded in the eCRF. The reason for antifungal medication and the outcome of treatment will also be recorded. Chemotherapy regimens (summary only) taken during the 12 weeks prior to study screening will be recorded. All other medications taken during the 4 weeks prior to study screening will be recorded. Concomitant medications will be recorded during the main study phase and extended treatment phase of the study, and during the associated FU and ET FU periods.

Prior and concomitant non-antifungal medication to be reported throughout the course of the study as follows:

- All chemotherapy regimens (summary only) taken during 12 weeks prior to screening.
- All T-cell immune-suppressants (e.g. cyclosporine, tacrolimus, monoclonal antibodies or nucleoside analogues) given within 90 days prior to screening or any dosing prior to study entry that support the host factor criteria “Treatment with other recognized T-cell immunosuppressants” at the time of the initial diagnosis of the fungal infection.
- All other medications given within 4 weeks prior to screening or any dosing prior to study entry that support the host factor criteria “Prolonged use of Corticosteroids”.
- All medications taken during the treatment period.
- All medications taken during the 4-week post-treatment period.

All concomitant medications taken by the patient during the study (including the 4-week FU period) are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration and indication of each drug. Concomitant antifungal medication must be recorded. Non-medication procedures (e.g., radiation therapy, surgery), including all treatment for IFD, and any changes to a concomitant medication or other intervention should also be recorded in the appropriate section(s) of the eCRF.

### 5.9.1 Excluded Medications

Concomitant administration of teriflunomide and leflunomide is prohibited as the risk for combined hepatotoxicity with these inhibitors of human DHODH is not known. There are no other absolutely prohibited or contraindicated medications. [redacted]

#### 5.9.1.1 *Agents with a potential effect on the QT interval*

Concentration-QTc effect modelling using data from a healthy volunteer study, where F901318 was administered orally for 18 days at a maintenance dose level of 240 mg twice daily, has shown no evidence of a clinically significant effect of F901318 on cardiac repolarization at a supratherapeutic exposure. The pharmacokinetic-pharmacodynamic model predicted no clinically significant effects on QTc at the mean steady state $C_{max}$ of 4.8 µg/mL achieved in this study (mean $C_{max}$ of < 4 µg/mL is predicted in Study F901318/0032). However, as Study F901318/0032 is the first clinical study in patients with invasive fungal infections, precautionary measures will be taken.

Prior to study start, if a patient is receiving a stable dose of a medication with the potential to prolong the QT/QTc interval and the patient has QTcF < 500 msec, they will be eligible for enrolment in the study.

Guidance for management of the initiation of a QT-prolonging agent after enrolment is currently under review. At present initiation of treatment with any medication with the potential to prolong the QT/QTc interval after treatment with F901318 has commenced is only permitted after discussion with the MM. Based on guidance contained in the medical monitoring plan current at the time, the MM will advise on required ECG monitoring (if any). Such monitoring may include:

[redacted]

[redacted]

[redacted]

#### 5.9.1.2 *Interaction of F901318 with Concomitant Medication*

Medications with the potential for meaningful DDIs with F901318 are summarized in the IB and in this section. In brief, any agent that either inhibits CYP-mediated drug clearance (might reduce clearance of F901318) or that is cleared by CYP3A4 (levels might be increased by F901318) should be used with care. [redacted]. All other medications with potential for DDIs should be approached on a case-by-case basis in consultation with the MM.

In *in vitro* studies, F901318 is a substrate for CYP1A2, CYP2D6, CYP2C19, CYP3A4, CYP2C9, and CYP2C8, with metabolism being more significant for 3A4, 2C9, and 2C8. F901318 is not an inducer of any CYP enzyme. F901318 is a weak inhibitor of CYP3A4 (clinical studies have shown an approximate 1.6-fold elevation of midazolam exposure). F901318 also shows potential for inhibition of the P-gp, BCRP, and BSEP transporters in *in vitro* studies, and whilst the potential for drug interactions is thought low, careful monitoring may be needed for sensitive substrates of these transporters which have narrow therapeutic windows. The specific combination of F901318 and fluconazole (CYP3A4 and CYP2C9 inhibitor) has been studied in man and fluconazole has been shown to increase mean $AUC_{0\text{-}12}$ and $C_{max}$ of F901318 by 2.0 and 1.7-fold, respectively.

[redacted] In addition, F901318 could increase the exposures of compounds metabolized by CYP3A4.

The Investigator is advised to consult with the MM on concomitant medications that either are metabolized by the liver or that influence hepatic metabolism, [redacted]. Specific data on other drug-drug combinations is being continuously developed. [redacted]

#### 5.9.1.3 *Co-Dosing with Strong CYP Inducers*

Due to potential DDIs with F901318 and CYP inducers, co-dosing with these agents may lead to CYP induction that could dramatically reduce F901318 levels. [redacted] Consultation with the MM is advised if the combination of F901318 with a CYP inducer cannot be avoided.

Strong CYP inducers include :

- Phenytoin
- Rifampin
- Flucloxacillin (Kennedy 2015; Muilwijka 2017)
- Dicloxacillin
- Nafcillin
- Carbamazepine
- Ritonavir (*note that ritonavir is both an inducer and an inhibitor*)
- Enzalutamide
- Mitotane
- St John's wort

See also further guidance on strong CYP inducers at the FDA website: (https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm).

If a medication that potentially induces CYP is required, consultation with the MM is advised. An extra visit for Unscheduled Trough PK sampling for rapid analysis will be required after starting or stopping such concomitant medication, to support evaluation of the impact of the potential DDI.

The Unscheduled Trough PK samples will be sent to the regional hub for rapid trough PK analysis of F901318 to enable assessment of potential DDIs.

#### 5.9.1.4 *Co-Dosing with CYP Inhibitors*

Monitoring of circulating levels of F901318 is required when co-dosing with CYP inhibitors.

As F901318 is metabolized by CYP3A4 and CYP2C9 there is a potential for DDIs. Co-dosing with CYP3A4 inhibitors may increase exposure to F901318. *In vitro* data suggest that metabolism by other CYPs is limited. Consultation with the MM is advised if the combination of F901318 with a CYP3A4 inhibitor cannot be avoided.

Where use of concomitant medication has been approved, an extra visit for Unscheduled Trough PK sampling will occur 3 to 5 days after starting or stopping such concomitant medication. This Unscheduled Trough PK sample will be sent for rapid trough PK analysis of F901318, to support evaluation of the impact of the potential DDI.

The Unscheduled Trough PK samples will be sent to the regional hub for rapid trough PK analysis of F901318.

[redacted]

[redacted]

#### 5.9.1.5 *Co-Dosing F901318 with Sensitive and Moderately Sensitive CYP3A4 Substrates*

Monitoring of circulating levels of the concomitant medication is required when co-dosing F901318 with sensitive and moderately sensitive CYP3A4 substrates.

F901318 is a perpetrator of potential DDIs with CYP3A4 substrates. As F901318 is a weak inhibitor of CYP3A4, co-dosing with sensitive and moderately sensitive CYP3A4 substrates may increase exposure of these substrates. Consultation with the MM and use of TDM for the substrate are advised if the combination cannot be avoided.

For those concomitant medications which are sensitive and moderately sensitive CYP3A4 substrates and which undergo routine TDM (such as transplant drugs), changes in concomitant drug treatment and all TDM results for the concomitant medication will be recorded. If the patient is receiving the concomitant medication prior to receiving F901318, a baseline TDM sample should be sent for analysis prior to F901318 treatment commencing. Further TDM sampling should be performed on a schedule based on the Investigator's judgment regarding the given medication.

**Sensitive substrates:** alfentanil, avanafil, budesonide, buspirone, conivaptan, cyclosporin, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lovastatin, lurasidone, maraviroc, midazolam,

naloxegol, nisoldipine, quetiapine, ruxolitinib, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, and vardenafil.

**Moderately sensitive substrates:** alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil.

See also further guidance on sensitive and moderately sensitive CYP3A4 substrates at the FDA website.

### 5.9.2 Allowed Medications

See Section 5.9 for a general discussion of concomitant medications.

#### 5.9.2.1 *Candida Prophylaxis and Concomitant Antifungal Therapy*

F901318 is not active against yeast infections and the use of fluconazole for prophylaxis or treatment of concomitant candidiasis is permitted at any time due to fluconazole's lack of activity against mould fungi. Patients who are receiving treatment with isavuconazole or posaconazole should be switched to receive treatment with fluconazole. Should a patient start or stop receiving fluconazole treatment whilst on study, an extra visit for Unscheduled Trough PK sampling will occur 3 to 5 days after starting or stopping such concomitant medication. This Unscheduled Trough PK sample will be sent for rapid trough PK analysis of F901318, to assess the impact of any dose adjustment made.

In order to meaningfully analyse the efficacy of F901318, it is important to avoid concomitant use of other systemic antifungal agents with known or potential activity against the primary fungal infection. That said, the constraints on choice of additional agents may be complex and thus use of any other systemic concomitant antifungal or combination treatment (such as addition of terbinafine for confirmed *Lomentospora prolificans* infections or an echinocandin to manage infection due to Candida) is permitted but is discouraged.

For all other infections, antifungal combinations should be based on the Investigator's clinical judgement with efforts made to minimize use where possible. Use of concomitant antifungal therapy must be discussed and agreed with the MM.

## 5.10 Medical Care of Patients after End of Study

The EOS for each patient is defined as the last assessment (scheduled or unscheduled) assigned to the study which that patient completes.

The Sponsor will not provide any additional care to patients after they discontinue F901318 therapy under this protocol because such care should not differ from what is normally expected for patients with IFD.

## 5.11 Treatment Compliance

Study drug must be administered in accordance with the dose and frequency schedule as described in Section 5.1. Any departures from the intended regimen must be recorded in the eCRF. The Sponsor will inform the Investigator in writing of any changes to the study treatment regimen resulting from ongoing review of study data by the IDSMB. Any Investigator-initiated changes to the study treatment regimen resulting from clinical assessments must be discussed with the MM and approved by the MM.

At each visit, prior to dispensing study drug tablets, previously dispensed study drug tablets will be retrieved by the Investigator or designee and compliance assessed. Patients exhibiting poor compliance should be counselled on the importance of good compliance to the study dosing regimen, and the reason for poor compliance should be investigated. Proper instructions on drug dosing must be provided to the patient by the Investigational staff.

The time of each oral dose will be recorded in a patient dosing diary. Patients who participate as an out-patient at any time on the study will be given the drug dosing diary to take home and complete. Proper instructions on drug dosing and diary completion must be provided to the patient by the Investigational staff. This diary will be reviewed by site staff at each oral drug dispensing visit.

## 5.12 Study drug Accountability

The Investigator, a member of the investigational staff, or a hospital pharmacist must maintain an adequate and current record of the receipt and distribution of all study drug using the Drug Accountability Form. These forms must be available for inspection at any time.

The Investigator or designee is responsible for recording the date of first and last study treatment administration. The Investigator or designee is also responsible for recording the details required to perform drug accountability and compliance assessments:

- Oral - number of tablets dispensed and the number of tablets returned at each visit, missed doses (including cases of vomiting that may affect dosing) and the reason

Dosing interruptions are to be avoided but may be necessitated by patient care circumstances. The reason for dosing interruption should be recorded wherever possible.

All empty tablet bottles must be kept at the pharmacy or at a place where the study monitor has access to perform drug accountability.

For Out-Patients, oral medication will be supplied in bottles sufficient for 2 weeks of dosing. A maximum of 4 weeks of dosing may be supplied to a patient at any given time without Sponsor approval up to the end of the 84 to 90 day main study phase. Requests for supply to cover more than 4 weeks of dosing will be considered on a case by case basis and must be approved by the Sponsor prior to being supplied to the patient. For those patients receiving ET beyond 84 to 90

days, sufficient medication may be supplied for 8 weeks of dosing. Unused medication may be returned to the patient at the ET visits, to ensure the patient has sufficient study drug to cover possible delays between ET visits. During the informed consent process, the Investigator should discuss with the patient the need to return to the study site between visits for oral drug re-supply. Patients will be given an oral drug dosing diary to take home and complete. This diary will be reviewed by site staff at each oral drug dispensing visit.

All study drug supplies should be accounted for at the termination of the study and a written explanation provided for discrepancies. Patients receiving ET beyond Day 90 should switch to use of drug supplied by that mechanism. All unused study drug supplies and packaging materials are to be inventoried and either returned to [redacted] by the Investigator or destroyed locally if suitable facilities are available. The Investigator is not permitted to return or destroy unused clinical drug supplies or packaging materials unless authorized by [redacted]

Further details on drug accountability are outlined in the Pharmacy Manual. Study medication must not be used for any purpose other than the study. Study medication must not be used after the retest date unless the study medication is reassessed and its release date extended.

# 6.0 ASSESSMENTS AND PROCEDURES

The objectives of the study are to describe the efficacy, safety and tolerability 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. For the schedule and timing of efficacy and safety assessments, see Table 1.

Assessments of the F901318 PK profile include trough (pre-dose) concentrations to be evaluated throughout treatment, and Intensive PK to be evaluated across a dosing interval [redacted] For the schedule and timing of PK assessments, see Table 2.

## 6.1 General Considerations

### 6.1.1 Schedule of Assessments

Day 1 is defined as the first day of administration of study drug. There is no Day 0; Day -1 is the day before administration of first dose of study drug, days preceding this are Day -2, Day -3, etc. Day 2 is the second day of administration of study drug, Day 3 is the third day of administration of study drug, etc.

Study assessments (visits) are scheduled in relation to days of administration of study drug. Screening assessments are to be completed within the 7 days prior to start of treatment unless otherwise specified and agreed with the MM. Assessments scheduled between Day 1 and Day 10 must be completed within the scheduled windows. Subsequent visits are permitted some flexibility to facilitate completion of the assessments; ± 2 days for the visits between study Day 14 and study Day 35 (Visits 8 to 12a) and ± 3 days at study Days 42, 49, 56, 70 and main study phase EOT (Visits 13 to 15, and 17). The Day 84 assessment (Visit 16) is permitted ± 6 days to allow treatment up to Day 90. The post-treatment FU visit (Visit 18) will be performed 4 weeks (±7 days) after the last dose of study drug (this may not be the last patient visit). 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. Subsequent visits will be every 4 weeks to assess the safety of continued treatment and to assess the need for further treatment, and there will be a FU visit 4 weeks after ET is completed.

### 6.1.2 Informed Consent

Written informed consent must be obtained prior to performing any study specific assessments in accordance with the inclusion criterion described in Section 4.3.1. Procedures that are part of standard care may occur before informed consent is obtained.

A separate informed consent is required for those patients who receive ET beyond Day 90, in accordance with the inclusion criterion described in Section 4.3.1.1.

## 6.2 Procedures

### 6.2.1 Demography

At screening, the following demographic characteristics will be recorded in the eCRF: patient initials, gender, race, ethnicity, date of birth. Demographic data collection will be done in accordance with local regulations. Height and body weight will also be recorded.

It is not known if the efficacy or safety profile of F901318 is influenced by race or ethnicity. Recording race and ethnicity in this study will facilitate future evaluation of the potential influence of these factors on the safety and efficacy profile of F901318. The patient will be informed that race and ethnicity will be recorded, and that collection of this information is voluntary.

### 6.2.2 Pregnancy Test

At screening, all female patients of childbearing potential will submit a urine or serum sample for a human chorionic gonadotrophin pregnancy test that will be analysed locally. Female patients complying with all other eligibility criteria must have a negative pregnancy test to be enrolled into the study.

If the patient is not hospitalised, additional pregnancy tests will be required [redacted] in the main study phase visits. The result of the pregnancy test will be recorded in the eCRF.

If the patient is not hospitalised, pregnancy tests will be required at the visits every 4 weeks for patients who receive ET and at the FU visit 4 weeks after the last dose of F901318. The result of the pregnancy test will be recorded in the eCRF.

### 6.2.3 Underlying Disease or Condition

At screening, all underlying diseases or conditions that predispose the patient to IFD will be recorded in the appropriate section of the eCRF.

Information to be collected will include the diagnosis for the underlying disease, type of chemotherapy received, whether the patient has received a bone marrow transplant or organ transplant, steroid use and duration, duration of neutropenia, antifungal prophylaxis and duration.

### 6.2.4 Infectious Disease History and Microbiological Assessments

**Fungal**

History of all fungal infections (including the IFD under study) within the 6 months prior to study drug administration. All history relating to the study-qualifying infection should be recorded, regardless of the time prior to study drug administration. For mycological assessments and responses, please refer to Section 6.3.1.4.

**Viral**

History of all viral infections within the 6 months prior to study drug administration.

All virology assessments performed within 6 months prior to the first administration of study drug, during the study and including the 4 weeks post-treatment period will be recorded.

**Bacterial**

History of all bacterial infections within 1 month prior to study drug administration.

For bacteriology, all assessments yielding bacterial growth performed within 1 month prior to the first administration of study drug, during the study and including the 4 weeks post-treatment period will be recorded.

### 6.2.5 Medical History

At screening, all existing clinically significant baseline conditions and/or clinically relevant medical conditions occurring within the 3 months prior to study drug administration will be recorded in the appropriate section of the eCRF. In addition, major medical history occurring at any prior time should be recorded, e.g. there is no time restriction for recording previous medical conditions with the potential to affect immune status.

### 6.2.6 Prior and Concomitant Medication

Prior medication will be reported in the eCRF as follows:

- All T-cell immunosuppressants (e.g. cyclosporine, tacrolimus, monoclonal antibodies or nucleoside analogues) given within 90 days prior to screening or any dosing prior to study entry that support the host factor criteria “Treatment with other recognized T-cell immunosuppressants” at the time of the initial diagnosis of the fungal infection.
- All chemotherapy given during 12 weeks prior to screening (summary of regimens should be provided).
- All other medications given within 4 weeks prior to screening or any dosing prior to study entry that support the host factor criteria “Prolonged use of Corticosteroids”.
- All medications taken during the treatment period.
- All medications taken during the 4-week post-treatment FU period.

In the eCRF, prior and concomitant antifungal medication will be recorded separately from other prior and concomitant medications.

### 6.2.7 Non-medication Procedures

All non-medication procedures (e.g. radiation therapy, blood transfusions, dialysis,surgery) received within 2 weeks prior to the first dose of study drug, during the treatment period or during the 4 weeks post-treatment FU period will be recorded in the appropriate section of the eCRF.

### 6.2.8 Hospitalization Status

The reason, date of admission and discharge, type of ward (intensive care unit, non-intensive care unit) and any changes in any of these parameters will be recorded in the eCRF from screening up to the end of the 4 weeks post-treatment FU period. Details of the definition of hospitalization and when hospitalization is not considered to be an SAE are given in Section 6.4.1.

## 6.3 Efficacy Assessments

The key efficacy measure for each patient will be the combination of improvement in clinical findings combined with changes in the diagnostic assay(s) used prior to study enrolment to determine the eligibility of the patient to receive treatment with F901318. It is essential that the same methodology, where possible, is used for the diagnostic assessments at baseline and for efficacy assessment during treatment to enable a valid evaluation of the response to treatment. Any additional assessments performed during the course of the study to assess the patients status may also be used to support efficacy response assessments.

All efforts should be made to have main study phase EOT assessments performed in all patients.

Patients with a successful overall outcome at the main study phase EOT that is prior to Day 42 must return for Day 42 and Day 84 Visits, even if they are no longer on study treatment. If administration of systemic antifungals as prophylaxis is anticipated following successful therapy patients should remain on study drug through Day 42.

Patients with an unsuccessful overall outcome at the main study phase EOT and requiring alternative systemic antifungal therapy will not be asked to return for Day 42 and/or Day 84 Visits; however the survival status at these timepoints will be collected at a minimum (confirmation by phone contact is acceptable and will be documented in the eCRF). For patients who complete treatment during the main study phase, a Follow-Up Visit will be performed 4 weeks after the last dose of study drug.

For patients who receive ET, subsequent visits in the ET phase will be every 4 weeks to assess the safety of continued treatment and to assess the need for further treatment, and there will be a FU visit 4 weeks after ET is completed.

### 6.3.1 Investigator's Assessment of Overall Response

Diagnostic assessments used to support the Investigators assessment of response include mycological culture, histology/cytology, GM, PCR, other mycology assessments, bronchoscopy and radiology tests used to confirm enrolment of the patient. It is essential, where possible, that the same methods are used for both diagnosis and assessment of overall response. Any additional assessments performed during the course of the study to assess the patients status may also be used to support efficacy response assessments.

The Investigator's assessment of response will be recorded at Day 7, Day 14, Day 28, Day 42, Day 84/EOT main study phase and 4 weeks after EOT in the main study phase. The Investigator will provide his/her opinion of the patient's response, based on the efficacy criteria as described in Section 6.3.1.1 (clinical), Section 6.3.1.2 (radiological), Section 6.3.1.3 (bronchoscopic), Section 6.3.1.4 (mycological) and Section 6.3.1.5 (overall response).

For patients who receive ET with F901318, the Investigator's assessment of overall response will be recorded at each visit to support continued treatment.

If multiple fungal mould pathogens are present, the DRC will separately analyse outcome for each relevant pathogen. Pathogens which were known at baseline to be F901318-resistant and for which alternative concomitant therapy was provided are not separately scored by the DRC. For example, a patient treated with F901318 and isavuconazole for simultaneous azole-resistant aspergillosis and mucormycosis would receive an overall score only for the response of the aspergillosis. As appropriate, the Investigator may provide per-fungus comments on the clinical, radiological, and mycological elements but per-fungus scores for each of these sub-elements are not required.

#### 6.3.1.1 *Clinical Response*

Clinical response will be based on clinical signs, physical findings, and symptoms relevant to each patient. The Investigator will be responsible for identifying and assessing clinical signs, physical findings, and symptoms related to the IFD reported for each patient. Assessment of clinical response will be based on changes from baseline signs, findings, and symptoms. Clinical signs, physical findings, and symptoms will be assessed [redacted] as shown in Table 1. Assessment at Day 42 and at Day 84 is required for all patients, including those who completed treatment before these visits.

For patients who receive ET with F901318, the Investigator's assessment of clinical response will be recorded at each visit to support continued treatment.

Baseline symptoms may need to include symptoms present at the time of the initial diagnosis of the qualifying infection. This situation may arise when a patient has had a prior therapy, responded to that therapy, but then developed intolerance to the therapy and is hence started on F901318 therapy without active symptoms at the point of study enrolment. Such prior symptoms will be recorded in the appropriate section of the eCRF.

The results of assessments of clinical signs, physical findings, and symptoms (including those performed outside of these mandatory scheduled timepoints) will be recorded in the eCRF.

An assessment of the patient's clinical response (all non-radiological clinical signs, physical findings, and symptoms related to IFD) will be recorded [redacted]

*(Note that 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.)*

- **Resolution-Complete:**
  For patients with attributable clinical symptoms and physical findings of IFD present at baseline, Resolution-Complete is assigned if
  a) there is resolution of all attributable clinical symptoms and physical findings of IFD present at baseline or that appeared at a subsequent prior visit
     AND
  b) no new clinical symptoms and physical findings of IFD are noted at the current visit.

  For patients lacking attributable clinical symptoms and physical findings of IFD present at baseline*, Resolution-Complete is assigned if
  a) there is resolution of all attributable clinical symptoms and physical findings that appeared at a subsequent prior post-baseline visit
     AND
  b) no new clinical symptoms and physical findings of IFD are noted at the current visit.
     AND
  c) patient meets mycological criteria for Eradication or Presumed Eradication

- **Resolution-Partial:**
  For patients with attributable clinical symptoms and physical findings of IFD present at baseline, Resolution-Partial is assigned if
  a) there is some persistence of the attributable clinical symptoms and physical findings of IFD noted either at baseline or at a subsequent prior post-baseline visit but there is improvement in at least some of these same symptoms and findings
     AND
  b) no worsening of any of these same symptoms and findings
     AND
  c) no new clinical symptoms and physical findings of IFD at the current visit.

  For patients lacking attributable clinical symptoms and physical findings of IFD present at baseline*, Resolution-Partial is assigned if
  a) there is some persistence of the attributable clinical symptoms and physical findings of IFD noted at a subsequent prior post-baseline visit but there is improvement in at least some of these same symptoms and findings
     AND

b) no worsening of any of these same symptoms and findings
AND
c) no new clinical symptoms and physical findings of IFD at the current visit.
AND
d) patient meets mycological criteria for Eradication or Presumed Eradication.

** If the qualifying infection was diagnosed before baseline, data regarding the prior symptoms and prior evaluation(s) of the invasive fungal infection may need to be considered.*

- **Failure-Stable:** Neither worsening nor improvement in any attributable clinical symptoms and physical findings present at baseline or that appeared at a subsequent prior visit AND no new clinical symptoms and physical findings of IFD at the current visit.
- **Failure-Progression:** Shows EITHER worsening in one or more attributable clinical symptoms and physical findings present either at baseline or that appeared at a subsequent prior visit OR appearance of new clinical symptoms and physical findings of IFD at the current visit.
- **Results not available**/patient unevaluable (i.e. visit and/or assessment of clinical symptoms and physical findings of IFD was not performed).

Note that the rules defining success are tested in sequence beginning with Success-Complete.

#### 6.3.1.2 *Radiological Response*

As relevant for the IFD under study, baseline radiological assessments of IFD should be performed during the screening period and during the course of the study. The assessment of the patient's radiological response related to IFD will be recorded at [redacted] as clinically indicated. Note that radiological response assessments can be made using all available radiology since the last response assessment visit or within the visit window of the visit in question.

Radiological assessments of IFD should be made in accordance with local practice and as clinically indicated. The same methodology should be used for each radiological assessment performed for a patient throughout the study. All radiological images taken up to Day 84/Day 90 and the post-treatment FU must be forwarded to the appropriate central reading laboratory for independent review. Images taken during ET or at the post-ET FU should not be sent for independent review. Further details will be provided in a Central Reading Laboratory Manual, including instructions for recording and shipping of radiological images.

The results of all IFD-related radiology performed during the study will be recorded in the eCRF and the reports will be collected.

Radiological response for all pathogens will be described as:

- ≥ 90% improvement in aggregate (across all lesions if more than one lesion)
- ≥ 50 to < 90% improvement in aggregate (across all lesions if more than one lesion)
- ≥ 25% to < 50% improvement in aggregate (across all lesions if more than one lesion)
- No change (0%) to < 25 % improvement in aggregate (across all lesions if more than one lesion)
- Worsening in aggregate (across all lesions if more than one lesion)
- No signs on radiological images at screening
- Results not available (i.e. visit and/or radiological assessment was not performed at the scheduled timepoint [Day 7, Day 14, Day 28, Day 42, main study phase EOT, Day 84 or 4-week FU]). This category is only applicable if there was no radiology performed since the last response assessment visit.

*(Note that 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).*

#### 6.3.1.3 *Bronchoscopic Assessment*

Bronchoscopy should be performed as clinically indicated, in accordance with local practice, and samples should be obtained for culture and histology/cytology testing during the same procedure. If bronchoalveolar lavage (BAL) samples are taken for local GM and PCR testing, additional aliquots must be obtained for shipping to the appropriate central laboratory. This applies for all respiratory samples taken up to the Day 84/Day 90 visit and the post-treatment FU visit, but samples for central laboratory assessment are not required during ET or at the post-ET visit.

#### 6.3.1.4 *Mycological Assessments and Responses*

Mycological criteria to be used for enrolment of patients are described in Appendix 2. Mycological assessments include culture, histology/cytology, GM (in the case of IA), PCR, and other mycology assessments depending on the IFD under study. Mycological assessments will be performed according to local practice using local laboratories and central laboratories up to the Day 84/Day 90 visit and the post-treatment FU visit, but samples for central laboratory assessment are not required during ET or at the post-ET visit.

Samples to be assessed include those suitable for fungal culture and isolation and/or biopsy or biological fluid samples from the infected site for histology/cytology, GM, and PCR. For each sample obtained, an additional sample must be collected for shipment to the appropriate central laboratory.

If available, baseline pathogen isolates, tissues, or biological fluid samples associated with the IFD will be stored and shipped to the appropriate central laboratory for confirmation of infection, identification of the fungal species, and susceptibility testing. Any available pre-study (baseline) isolates, tissues, or biological fluid samples should be shipped regardless of date of collection relative to study initiation. If infection is due to multiple fungi, relevant isolates, tissues, or

biological fluid samples for all infecting species should be shipped. Materials relating to yeast isolates do not need to be shipped.

*If it is not possible to send isolates, tissues, or biological fluid samples to confirm the EORTC classification, where available, relevant digital images should be submitted to the appropriate central laboratory for review. If there are no isolates, samples or images available for shipment to the central laboratory, local laboratory reports confirming the EORTC criteria will be used to support the EORTC classification. Local laboratory report details documenting the EORTC classification for ALL patients should be submitted to the eCRF.

If the identities of the pathogens differ between the central and local laboratories, the central laboratory results will take precedence over the local results for all study purposes.

Guidelines for collection, culture and shipping of fungal isolates and handling of other samples (for GM and PCR) will be provided in the Central Laboratory Manual.

The results of all mycological assessments performed during the study will be recorded in the eCRF.

**Culture:** Isolates obtained by culture should be sent to central laboratory testing. Please refer to the laboratory manual for shipping details for fungal cultures as shipping details vary depending on the organism under study. Considerations for culture include:

- Suitable samples for fungal culture and isolation (blood/CSF/tissue cultures).
- Follow-up culture samples from non-bloodstream infections, if obtained, results should be recorded.
- For outcome assessment of fungal blood stream infections, confirmed (two consecutive) negative blood cultures are required.
- All isolates should be identified to species level.
- Biopsy/biological fluid samples from the infected site for histology and cytology.
- If patient has LRTD and is able to produce sputum, samples should be sent for culture and histology / cytology.

All baseline and main study phase EOT isolates will be stored and shipped for central retesting. Due to the nature of the relevant infections, baseline isolates may include cultures collected weeks or months before enrolment. The central laboratory results will be considered definitive.

**Galactomannan Antigen**: Galactomannan (GM) is a cell wall polysaccharide component of *Aspergillus* species that can be detected in serum samples using an immune-enzymatic sandwich micro-plate assay (Platelia™ Bio-Rad assay), with results expressed as an optical density index. This assay has been approved by the FDA, with a serum GM index of ≥1.0 or two consecutive

values each of ≥0.5 (i.e., from 2 separate blood draws) as the cut off for positivity. Further details of the criteria relating to GM values and the restrictions that should be applied in relation to this assay are provided in Appendix 2.

All sites with the capability to perform serum GM testing locally should split samples for serum GM analysis into 2 aliquots, and send 1 aliquot for local testing and 1 aliquot to the appropriate central laboratory for testing. These specimens will have the same date and time of collection noted in the eCRF.

For all patients with IA, GM testing must be conducted [redacted]. If Screening and Day 1 occur on the same day 2 serum GM samples should be obtained pre-dose, at least 1 hour apart. Screening GM samples must be taken within 10 days prior to the first dose of study drug. Local laboratory results of serum GM obtained within 10 days prior to the first dose of study drug may be used to support the 'probable IA' eligibility criteria and must be reported in the eCRF.

BAL GM (*Aspergillus* only): Values ≥1.0 (2 aliquots of the same sample should be tested) will be assessed as a positive result for Probable LRTD IA. Culture and histology must be obtained from the same sample and serum GM must be obtained in accordance with the protocol. Plasma-LyteTM (Baxter) may not be used as the lavage fluid.

**Polymerase Chain Reaction Assay**: The polymerase chain reaction (PCR) assay is widely used as a diagnostic tool in clinical laboratories as an aid in the diagnosis of IFD. When diagnosis of the pre-study fungal infection is based on or supported by PCR findings, additional samples must also be provided for PCR testing by the appropriate central laboratory.

**CSF Findings for Coccidioidomycosis Patients:**

a. The analysis of CSF is widely used as a diagnostic tool in clinical laboratories as an aid in the diagnosis of Coccidioidomycosis. Further details of the criteria relating to CSF testing for study entry are provided in Appendix 2.

b. When diagnosis of the pre-study fungal infection is based on or supported by CSF findings, additional samples collected during the study must also be provided for CSF serology testing by the appropriate central laboratory. If baseline samples are not available for shipment to the appropriate central laboratory, patient eligibility will be based on local laboratory findings.

c. Even if local CSF coccidioidal serodiagnostic testing is available, an aliquot should be shipped to the appropriate central laboratory for testing. These specimens will have the same date and time of collection noted in the eCRF.

d. Other CSF findings supportive of a coccidioidomycosis diagnosis (e.g. protein elevation, low glucose etc.) will be collected and reported in the eCRF.

**Mycological Response**

The Investigator will be asked to provide an assessment of the mycological response for each patient at Day 7, Day 42, Day 84/EOT and 4 weeks after EOT in the main study phase and at other visits as clinically indicated (*note that 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.* ). Outside of these timepoints, mycological assessment will be performed as clinically indicated and/or in line with standard clinical management for the patient's specific IFD and anatomic site involved.

The Investigator will provide an assessment of the mycological response as follows:

- **Eradication** (eradication of the original causative organism cultured or identified by histology/cytology at baseline and no emergence of new causative organisms at that visit).
- **Presumed eradication** (missing documentation of the eradication of the original causative organism cultured or identified by histology/cytology at baseline and no documentation of emergence of new causative organisms at that visit plus resolution of all or some attributable clinical symptoms and physical findings of IFD present at baseline and/or of those that appeared at a subsequent visit and no appearance of new attributable clinical symptoms and physical findings of IFD at that visit).
- **Persistence** (persistence of the original causative organism cultured or identified by histology/cytology at baseline or emergence of a new causative organism at that visit).
- **Presumed persistence** (missing documentation of the persistence of the original causative organism cultured or identified by histology/cytology at baseline and no documentation of emergence of new causative organisms at that visit plus either (i) no resolution or (ii) worsening of any attributable clinical symptoms and physical findings of IFD present at baseline and/or of those that appeared at a subsequent visit and/or appearance of new attributable clinical signs and physical findings of IFD at that visit).
- **No mycological Follow-up results available**, for whatever reason (no diagnostic test done at the scheduled timepoint AND other data are insufficient to support assigning Presumed Eradication or Presumed Persistence).
- **No mycological evidence at baseline** (negative diagnostic test(s) results at baseline, or not done at baseline).

**Mycological Response after Initial Success**

If relevant mycology findings occur after successful mycological response (proven or presumed eradication), an evaluation will be made as to whether the infection is recurrent (same species as at baseline) or emergent (different species compared with baseline). Patients with recurrent or

emergent infection will be classified as mycological failure from the visit onwards where positive cultures were reported.

**Recurrent** – Re-appearance of same species after apparent negative culture PLUS additional antifungal treatment becomes necessary.

**Emergent** – Appearance of new species after apparent negative culture PLUS additional antifungal treatment becomes necessary. New species emerging during the first 7 days of therapy with F901318 are presumed to have been present at baseline and are classified as Baseline secondary infections rather than Emergent infections.

#### 6.3.1.5 *Investigator's Assessment of Overall Response*

The Investigator's assessment of overall response will be based on all available assessments (clinical, radiological and mycological) as described in Sections 6.3.1.1, 6.3.1.2 and 6.3.1.4. It is essential that the same methods and assessments are used to define the IFD diagnosis at baseline and to evaluate the response to treatment.

**Treatment "success"** is defined as **complete** or **partial**.

**Treatment "failure"** is defined as **stable** response or **progression** of IFD.

Of the three components of overall response, only clinical and mycological responses are required. Patients who lack data at a visit (e.g., the visit data were not collected for some reason) or who are not evaluable at the visit because these data cannot be collected are considered failures.

The criteria for assessment of overall response are summarised in Table 5:

**Table 5 Criteria for Assessment of Overall Response**

| | |
|---|---|
| **Success - complete*:** | • Clinical: Meets criteria for Resolution-Complete;<br>AND<br>• Radiological (if assessed): Shows resolution of radiological abnormalities (≥90% response);<br>AND<br>• Mycological: Meets criteria for presumed or documented eradication. |
| **Success - partial*:** | • Clinical: Meets criteria for Resolution-Complete or Resolution-Partial;<br>AND<br>• Radiological (if assessed): Shows resolution or improvement of radiological abnormalities (at least 25% response);<br>AND<br>• Mycological: Meets criteria for presumed or documented eradication. |
| **Failure - stable:** | • Clinical: No improvement and no worsening of any attributable clinical symptoms and physical findings previously noted and no new attributable clinical symptoms or physical findings of IFD (Failure-Stable);<br>OR<br>• Radiological: Shows no evidence of progression OR < 25% improvement of radiological abnormalities;<br>OR<br>• Mycological: Had mycological evidence at baseline AND does not meet criteria for presumed or documented eradication. |
| **Failure - progression:** | • Clinical: Either worsening of attributable clinical symptoms or physical findings of IFD or appearance of new attributable symptoms or findings of IFD (Failure-Progression);<br>OR<br>• Radiological: Worsening or new radiological abnormalities;<br>OR<br>• Mycological: Has mycological evidence for a recurrent or emergent IFD, OR alternative systemic antifungal treatment required. |

*For these categories, the only required data are the clinical and mycological data. The absence of radiological evaluations at a given time point does not prevent assignment to Success-Complete or Success-Partial. The rules defining success are tested in sequence with Success-Complete assigned if its rules are met and Success-Partial otherwise assigned.

### 6.3.2 Survival

All-cause mortality has been used historically as an endpoint in other similar clinical studies in IFD. All-cause mortality will be assessed using survival status and, if applicable, death details will be recorded in the eCRF. If the patient has died, the date and cause of death will be recorded, in addition to details required for SAE reporting (see Section 6.4.1.2).

Survival status will be recorded at Day 42, main study phase EOT, Day 84 and at the 4-week FU and included in the CSR. Information on survival status on Days 42 and 84 will be collected in all

patients, irrespective of when treatment was discontinued *(note that 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)*.

Survival status will also be recorded at each ET visit and at the post-ET FU visit, and will be presented in the report addendum.

### 6.3.3 Data Review Committee Assessment of Overall Response

Independent assessment of overall response during the main study phase will be performed by the DRC for visits up to Day 84/Day 90, and for the post-treatment FU visit for patients who do not receive ET. The DRC will not assess overall response at any ET visits or at the post-ET FU. Details of the process and overall response definitions will be documented in the DRC charter.

### 6.3.4 Patient-Reported Outcomes

Patient-reported outcomes will be assessed in this study using the EQ-5D-5L questionnaire. The EQ-5D-5L questionnaire will be completed by the patient during screening to provide a baseline, at the Day 42 and Day 84/EOT main study phase visits, and every 4 weeks during the ET phase.

The questionnaire, translated as required in the local language, will be distributed by the site staff but completed entirely by the patient. To ensure instrument validity and that data standards meet health authority requirements, the questionnaire should be self-administered and checked for completion at the site staff prior to the completion of other study assessments.

## 6.4 Safety

The Investigator will evaluate safety by AE monitoring, physical examination, vital signs, laboratory tests, ECG, imaging and concomitant medication/surgery, as outlined in the Schedule of Assessments (Table 1 and Table 3).

### 6.4.1 Adverse Events

The Investigator is responsible for recording all AEs observed during the study period (main study phase and ET phase) including 4-week post-treatment follow-up.

Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or worsening of a preexisting condition (e.g., increase in its severity or frequency). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment. Lack of efficacy or insufficient clinical response should not be recorded as an AE.

Events which meet the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events which **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. **Changes in laboratory findings that fulfil the definition of an AESI must ALWAYS be reported as an AESI (AND as an SAE if any seriousness criteria are also met)**.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

<u>Definition of a Serious Adverse Event</u>

An SAE is any untoward medical occurrence (whether considered to be related to study drug or not) that at any dose:

- Results in death

- Is life-threatening (the patient is at a risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization: Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Other: Medically significant events, which do not meet any of the criteria above, but may jeopardize the patient and may require medical or surgical intervention to prevent one of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion) or convulsions that do not result in hospitalization.

An adverse drug reaction (ADR) is defined as any noxious and/or unintended response to a medicinal product related to any dose.

An unexpected ADR is defined as any adverse reaction, the nature of which is not consistent with the applicable product information. The Reference Safety Information Section of the IB identifies expected ADRs.

Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

Adverse Events of Special Interest

An AESI is defined as a serious or non-serious event of scientific and medical concern specific to the investigational product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is necessary.

All AESIs will be recorded on the Adverse Event form in the eCRF, and in source documents. Any AESI which occurs during this study, whether or not related to the study drug, must be recorded in the electronic data capture (eDC) system within 24 hours of study staff becoming aware of the event. This entry into the eDC system will automatically trigger an e-mail alert to the Sponsor and to the MM.

If for any reason it is not possible to record the AESI information electronically, i.e., the eCRF database is not functioning, record the AESI on the paper AESI reporting form and submit within 24 hours as described above.

As soon as it is possible to do so, any AESI reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.

Paper CRF reports are to be submitted to the Sponsor (or an authorized representative). Contact details for submitting paper CRF AESI reports will be provided to each site, including telephone number, fax number, and an e-mail address.

In addition to the initial 24-hour report, additional information is required to be added to the eCRF or a paper report sent to the Sponsor (or an authorized representative) within 48 hours of the event. These timelines apply to initial reports of AESIs and to all follow-up reports.

Based on the findings of nonclinical and clinical studies the following are classified as AESIs:

[redacted]

**Any hepatic AESI which meets biochemical Hy's Law criteria (i.e. ALT/AST > 3x ULN and total bilirubin > 2x ULN) or has transaminase elevations which meet CTCAE criteria grade 4 (i.e. ALT/AST> 20 x ULN), must be reported as a medically signficant SAE and as an AESI, regardless of causality.**

Please refer to the common terminology criteria for adverse event (CTCAE) V5.0 grading definitions (Table 6).

**Table 6 CTCAE Grading for Study AESIs**

| PARAMETER | GRADE 2: MODERATE | GRADE 3: SEVERE | GRADE 4: POTENTIALLY LIFE-THREATENING |
|---|---|---|---|
| [redacted] | | | |

## Severity

The severity of the AE will be characterized in accordance with CTCAE criteria (V5.0). If the AE is not defined by CTCAE criteria, the severity of the AE will be characterized as "mild, moderate or severe" according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe events interrupt the patient's usual daily activity.

**Relationship**

The causal relationship between the study drug and the AE has to be characterized as unrelated, unlikely, possible, probable or unknown (unable to judge).

Events can be classified as “unrelated” if there is not a reasonable possibility that the study drug caused the AE.

An “unlikely” relationship suggests that only a remote connection exists between the study drug and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the reported AE.

A “possible” relationship suggests that the association of the AE with the study drug is uncertain; however, the AE is not reasonably supported by other conditions.

A “probable” relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator’s clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state or concomitant medication reactions) do not appear to explain the AE.

All efforts should be made to classify the AE according to the above categories. The category “unknown” (unable to judge) may be used only if the causality is not assessable, e.g., because of insufficient evidence, conflicting evidence, conflicting data, or poor documentation.

All AEs encountered during the clinical study will be reported in the eCRF. If possible, a diagnosis should be documented rather than a list of individual signs and symptoms. All AEs should be recorded in English.

#### 6.4.1.1 *Reporting of Adverse Events*

All AEs which occur after the patient has provided informed consent, regardless of severity and whether or not they occurred during study enrolment, treatment or follow-up, are to be recorded on the appropriate AE pages (either ‘serious’ or ‘non-serious’) in the eCRF. The Investigator should complete all the details requested including dates of onset, severity, action taken, outcome and relationship to study drug. Each event should be recorded separately.

Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the Investigator should record this event in the eDC system within 24 hours of becoming aware of the event. This entry into the eDC system will automatically trigger an e-mail alert to the Sponsor and to the MM.

An event may qualify for expedited reporting to regulatory authorities if it is an SAE, unexpected per reference safety information and considered related (Suspected Unexpected Serious Adverse Reaction [SUSAR]) in line with relevant legislation. All Investigators will receive a safety letter

notifying them of relevant SUSAR reports. The Investigator should notify the Ethics Committee as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

Any SAE, including death due to any cause, which occurs during this study, whether or not related to the study drug, must be reported immediately (within 24 hours of the study centre's knowledge of the event) in the eCRF. The report will contain as much available information concerning the SAE to enable the Sponsor (or an authorized representative) to file a report, which satisfies regulatory reporting requirements.

If for any reason it is not possible to record the SAE information electronically, i.e., the eCRF database is not functioning, record the SAE on the paper SAE reporting form and submit within 24 hours as described above.

— As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.

— If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

Paper CRF reports are to be submitted by telephone or fax to the Sponsor (or an authorized representative). Contact details for submitting paper CRF SAE reports will be provided to each site, including telephone number, fax number, and an e-mail address.

In addition to the initial 24-hour report, additional information is required to be added to the eCRF or a paper report sent to the Sponsor (or an authorized representative) via fax or mail within 48 hours of the event. These timelines apply to initial reports of SAEs and to all follow-up reports.

All SAEs will be recorded on the SAE Report form, the Adverse Events form in the eCRF, and source documents. Criteria for documenting the relationship to study drug as well as severity and outcome will be the same as those previously described.

All SAEs that are spontaneously reported within 30 days of a patient's last visit (EOS visit) are to be collected and reported as previously described.

The information must include the following as a minimum:

- Name, address and telephone number of the reporting Investigator.
- Investigational product and study code.
- Patient identification number, initials, sex and date of birth.
- Description of the AE, measures taken and outcome.

- Preliminary classification of causal relationship by the Investigator.

In the case of fatal or life-threatening events, the Investigator should immediately telephone the Sponsor's Safety Surveillance and Reporting Unit (or an authorized representative). Contact details will be provided to the site. Additional follow-up information should be completed on an SAE follow-up form with a copy sent to the Sponsor (or an authorized representative) and the original placed in the SAE section of the eCRF binder.

#### 6.4.1.2 *Reporting of Serious Adverse Events to Regulatory Authorities and Investigators*

Investigators will be notified by the Sponsor (or an authorized representative) of all SAEs that require prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor (or an authorized representative). The Sponsor (or authorized representative) will ensure that all SAEs are reported to the appropriate regulatory authorities within the required timelines.

Any hepatic AESI which meets biochemical Hy's Law criteria (i.e. ALT/AST > 3x ULN and total bilirubin > 2x ULN) or has transaminase elevations which meet CTCAE criteria grade 4 (i.e. ALT/AST> 20 x ULN), must be reported as a medically signficant SAE, regardless of causality.

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB)/IEC, and Investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

A suspected unexpected serious adverse reaction is known as a SUSAR. The SUSAR, SAEs and other cases required by the concerned competent authorities will be reported by the Sponsor or the Sponsor's representative to all concerned parties within the prescribed timeframe. The Sponsor or representative will also submit periodic safety reports (e.g. Development Safety Update Reports) as required by international regulations.

#### 6.4.1.3 *Follow-up of Adverse Events*

Any AEs observed from the date of informed consent up to the EOS will be followed up to resolution. Resolution means that the patient has returned to a baseline state of health or the Investigator does not expect any further improvement or worsening of the AE. All AEs that occur after the patient completed a clinical study (within 30 days of the last dose of study drug) should also be reported to the Sponsor (or an authorized representative).

For hepatic AESIs, even though the AE may appear to have resolved, a longer follow-up may be requested by the HAC, in which case results of additional blood samples (analysed in a local laboratory for liver biochemistry) and other relvant clinical data will be collected and provided to the HAC for review.

For patients receiving ET, all AEs will be followed up to resolution.

#### 6.4.1.4 *Procedures for Documenting Pregnancy During Study*

Patients who are pregnant or expect to become pregnant during the course of the study will be excluded from participation in the study. Should a patient become pregnant after enrolling in the study, the Investigator will report this event to F2G or its designee within 24 hours and to the IRB/EC. No embryotoxicity or teratogenicity associated with F901318 treatment has been detected in the rat or rabbit. Nonetheless, as a new molecular entity, F901318 should not be given to pregnant women unless the benefit clearly outweighs the risk. The Investigator should consult with the MM to review any available new or supplemental information. The Investigator should then counsel the patient and discuss risks of continuing or discontinuing therapy with F901318, risks of continuing with the pregnancy and the possible effects on the foetus. Sites must request the patient's permission to query pregnancy outcome and follow each patient to determine the outcome of the pregnancy.

Results will be summarized in the CSR.

Patients who become pregnant at any point during the study (including during ET) should continue to be followed for safety assessments whether or not the patient is receiving further study treatments. Procedures that are contraindicated during pregnancy must not be performed. Investigators should use clinical judgment regarding subsequent study-related blood collection based on the presence or absence of anaemia in each patient. Patients who are not withdrawn from the study should continue to be followed for safety assessments to study discharge per protocol.

All pregnancies that occur from the time of the first screening procedure through the follow-up visits must be reported. Monitoring of the patient and the outcome of the pregnancy should be followed by the Investigator. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to F2G.

Male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant until the end of follow-up period. A Pregnancy Form should be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to Study Treatment. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will update the Pregnancy Form with additional information on the course and outcome of the pregnancy.

An Investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the foetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

The Investigator will follow the medical status of the mother, as well as the foetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried foetus)], the Investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is outlined below:

- “Spontaneous abortion" includes abortion and missed abortion
- Death of infant within 1 month after birth regardless of its relationship with study drug
- If infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the Investigator
- In case of a delivery of a living newborn, the "normality" of the infant is evaluated at birth
- "Normality" of the miscarried foetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

**Progression of Disease under Study**

Progression of disease under study (i.e. the qualifying fungal infection) will not constitute an AE. However, if the progression of disease leads to a serious outcome, such as death, this will be reportable within the same timeframe using the same format as for an SAE.

### 6.4.2 Clinical Laboratory Evaluations

The laboratory safety tests include haematology, biochemistry and urinalysis (including urine dipstick for protein and blood). Samples for the full clinical laboratory evaluation will be collected at as outlined in Table 1.

All blood samples for laboratory safety testing will be collected in the morning prior to administration of study drug and sent to the appropriate central laboratory where the testing will be performed.

In accordance with local practise, a duplicate sample will be taken and sent to a local laboratory for testing.

At Screening, local laboratory testing will be performed to determine patient eligibility. Laboratory tests for Screening should be obtained as close to the time of enrolment as possible. A list of clinical laboratory tests is provided in Table 7.

**Table 7 List of Clinical Laboratory Tests**

| | |
|---|---|
| **Serum Biochemistry** | |
| Albumin | Creatinine[a] |
| Alkaline phosphatase | Gamma glutamyltransferase |
| Alanine aminotransferase | Glucose (non-fasted)[b] |
| Aspartate aminotransferase | Potassium |
| Bilirubin (total and direct) | Prothrombin time and activated Partial Thromboplastin Time[c] |
| Calcium | Sodium |
| Chloride | Urea |
| Creatine phosphokinase | β-human chorionic gonadotropin in female patients (if applicable) |
| **Haematology** | |
| Absolute neutrophil count[d] | Platelet count |
| Haemoglobin | Red blood cells |
| Haematocrit | White blood cells and differential count (absolute values and percentages) |

a) For assessment of creatinine clearance.
b) Non-fasted is preferred and must be used consistently in each patient.
c) To be measured at baseline and Day 28, 56 and 84 or withdrawal and at the visits every 4 weeks for patients who receive ET.
d) For assessment of neutropenic status (see Section 6.4.2.2).

Samples of urine will be collected and analysed locally. Analysis of urine samples includes the dipstick for pH, glucose, blood and protein, and microscopic examination of sediment if dipstick test results are positive or strongly positive for blood or protein.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all timepoints throughout the study. The Investigator will evaluate any change in laboratory values. [redacted]. If the Investigator determines any other laboratory abnormality to be clinically significant, it is considered a laboratory AE and reported as an AE in the eCRF; however, if the abnormal laboratory value is consistent with a current diagnosis, it may be recorded accordingly in source documents but should not be reported in the

eCRF. Where appropriate descriptions have been developed, changes in laboratory test values will be assigned CTCAE severity grades, in accordance with National Cancer Institute (NCI) CTCAE version 5.0.

Details of central laboratory reference ranges, sample handling and shipment will be provided in the Laboratory Manual.

#### 6.4.2.1 *Creatinine Clearance*

At Screening, creatinine clearance will be calculated by the laboratory according to the Cockcroft-Gault formula, as shown below.

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age [years]}) \times \text{body weight (kg)}}{\text{Plasma creatinine (mg/dL)} \times 72} \times \text{Gender correction factor (male: 1.00; female: 0.85)}$$

#### 6.4.2.2 *Neutropenic Status*

Neutropenic status relating to the study-qualifying infection should be recorded, regardless of the time prior to study drug administration. Neutropenic status will be recorded for all patients for the period within 4 weeks prior to the screening visit. In addition, neutropenic episodes supporting the Host Factor criteria of "Neutropenia" related to the study-qualifying infection should be recorded, regardless of the time prior to study drug administration. Neutropenic status will be recorded throughout the main study phase and 4-week FU, and throughout the ET phase and post-ET FU for those patients who receive ET.

Absolute neutrophil count (ANC) will be used to determine neutropenic status, with neutropenia defined as ANC $< 0.5 \times 10^9$/L [$< 500/mm^3$]. The presence or absence of neutropenia and subsequent persistence or resolution (resolution defined as consecutive ANC values $> 0.5 \times 10^9$/L on two separate days) will be determined from the ANC values recorded in the eCRF.

All ANC values obtained (or calculated) at local laboratories during a neutropenic episode must be recorded in the eCRF with the corresponding sample dates. When differentials cannot be performed due to insufficient white blood cells (WBCs), the total WBC value must be recorded for that day in the eCRF.

#### 6.4.2.3 *Liver enzymes and bilirubin*

The Liver Biochemistry Management Algorithm (Appendix 3) provides guidance on the management of patients in the event that certain thresholds are met relating to increased levels of liver enzymes and/or bilirubin.

[redacted]

Whether taken as a protocol-scheduled sample as outlined in Table 1 [redacted] samples for assessments of liver enzymes and bilirubin are to be taken as duplicate samples with 1 sample to be sent to the appropriate central laboratory and 1 sample to be sent to the local laboratory. Samples taken during ET will be sent only to the local laboratory.

Patients must report immediately to the Investigator if there is onset of otherwise unexplained nausea, jaundice, right upper abdominal pain, fever, or rash, and a Full Liver Panel assessment must be conducted.

### 6.4.3 Vital Signs, Physical Findings and Other Safety Assessments

#### 6.4.3.1 *Vital Signs*

Assessments will comprise: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate and body temperature (C° or F°). Body temperature should be measured by the same method throughout the study. Vital signs will be assessed at the timepoints shown in Table 1, and the method (supine, sitting, or standing) should be consistently used for the same patient and will be recorded in the eCRF. During the study treatment period, vital signs will be assessed prior to study drug intake.

Body weight will be recorded [redacted] *(note that for patients who will 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 a FU visit 4 weeks after the last dose of F901318).*

No vital signs assessments will be recorded during ET, unless clinically indicated or associated with an AE.

#### 6.4.3.2 *Physical Examination*

A physical examination should be conducted at the timepoints shown in Table 1 and at any other time during the study when clinically indicated, as determined by the Investigator. The following body systems/areas should be examined: head, eyes, ears, neck, trunk, respiratory,

cardiovascular, gastrointestinal, musculoskeletal, neurological, endocrine/metabolic, lymphatic/haematologic, dermatological, psychological, genitourinary and other (to be specified). Any new abnormalities or worsening of existing abnormalities must be recorded in the eCRF as AEs.

Physical examination will not be recorded during ET, unless clinically indicated or associated with an AE.

#### 6.4.3.3 *Electrocardiogram*

A 12-lead electrocardiogram (ECG) recording will be obtained at the timepoints shown in Table 1. For patients receiving study drug (i.e., Day 1 onwards), the ECG assessment should be conducted between 30 minutes and 4 hours after oral dosing. All patients must also have an ECG at the main study phase EOT. At the Post-treatment Follow-up visit, ECG recordings will only be required for patients with abnormalities observed at the main study phase EOT.

Each abnormality observed on ECG must be reported and, if not related to the underlying disease, must be confirmed as clinically not significant or repeated at intervals determined by the Investigator until they return to baseline levels. Abnormalities should be reported as AEs in the eCRF only if they result in a clinically relevant condition, as determined by the Investigator. Each ECG recording is to be signed and dated by the Investigator or his designee.

Additional monitoring may be required if a QT-prolonging medication is initiated during the course of the study. See Section 5.9.1.1 for details.

Study-related ECGs are not required during ET, unless clinically indicated or associated with an AE.

#### 6.4.3.4 [redacted]

[redacted]

### 6.4.4 Safety Monitoring

#### 6.4.4.1 *Independent Data and Safety Monitoring Board*

An IDSMB consisting of members who are independent from the Sponsor will be established. The IDSMB will have at least 3 members. The IDSMB will be responsible for reviewing

outcomes, AEs and F901318 trough concentrations. The IDSMB will also review safety data for patients receiving ET. The first IDSMB meeting will be held after approximately 8 patients have completed treatment. The frequency of subsequent meetings will be decided by the IDSMB, but will be not less than every 6 months. The IDSMB may also meet in *ad hoc* meetings at its discretion as needed in response to events occurring in the study. Additional responsibilities for the Committee include confirmation of the safety and appropriateness of the selected dosing regimen. After each meeting, the IDSMB will recommend that the study can continue, or may recommend changes to the study or stopping the study.

Details of the membership and responsibilities of the IDSMB will be included in the IDSMB Charter.

#### 6.4.4.2 *Data Review Committee*

A DRC will be responsible for independent assessment of study data (see Section 8.13 for further details).

#### 6.4.4.3 *Hepatic Safety Review*

The hepatic-specific safety data from the Main Study Phase and from the Extended Treatment Phase of the study will be subject to review and surveillance:

- Narratives will be prepared for all hepatic AESIs (regardless of Investigator-assigned causality) which are subject to expedited review by the HAC.
- An Integrated Hepatic Safety Summary (a summary of hepatic safety across the entire clinical program) will be prepared at appporiate intervals for review by the HAC who will recommend, from a hepatic safety perspective, whether the study can continue or whether changes to the study are required. This report will also be provided to the IDSMB.

## 6.5 Pharmacokinetics (PK) and Rapid Trough Sample Analysis

**Pharmacokinetics**

Sampling for pharmacokinetic (PK) analysis will be performed in all patients.

The date and time of all blood sample collections for PK (Trough and Intensive PK) will be recorded in the eCRF. The date and time of the dose and meal given prior to each trough PK sample (scheduled and unscheduled) and prior to the start of intensive PK sampling, and date/time of any meals given during the Intensive PK sampling will also be recorded in the CRF. Full details regarding sample labelling, handling, shipping and storage will be outlined in the study laboratory manual.

A total of 3 categories of PK samples will be taken as follows:

1. **Trough PK Analysis**
   Samples for trough PK analysis will be taken within 15 minutes prior to the observed F901318 dose [redacted] The dose selected on each visit can be at the Investigator discretion. Samples will be split into 2 aliquots with 1 aliquot shipped to the regional hub for rapid trough PK analysis and 1 aliquot shipped to the appropriate central laboratory. For patients proceeding to ET, the Day 84 and main study phase EOT trough PK samples will be combined into a single trough sample at the time of the final visit for the main study phase. A sample for trough PK analysis will also be taken every 4 weeks during ET and shipped to the regional hub for rapid trough PK analysis.

2. **Intensive PK Analysis**
   Samples for assessing the PK profile of F901318 [redacted] will be evaluated in detail (Intensive PK) on [redacted] Timing of samples is relative to the oral dose. Recent (within the previous 7 days) and current concomitant medications will be fully documented to permit analysis of potential DDIs. These samples will be shipped to the appropriate central laboratory.

3. **Unscheduled Trough PK Analysis**
   Unscheduled Trough PK samples may be collected as needed in discussion with the MM (e.g., to evaluate drug-drug interactions). Trough samples will be taken within 15 minutes prior to an observed dose. These samples will be split into 2 aliquots with an aliquot shipped to (a) the regional hub for rapid trough PK analysis and (b) the appropriate central laboratory.

Samples shipped to the regional hub for rapid trough PK analysis (Scheduled and Unscheduled Trough PK samples) will be tested for F901318 alone. All PK samples (Scheduled and Unscheduled Trough PK, Intensive PK) will be shipped to the appropriate central laboratory and will be tested for both F901318 [redacted]

**Rapid trough PK analysis**:

Regional hubs will set up by the Sponsor for the rapid analysis all predose PK samples for F901318 (both Scheduled and Unscheduled). Dose adaptations may only be made in consultation with the MM when concomitant medications are required and the Investigator suspects there may a risk of a clinically relevant DDI or when the Investigator believes there may be sub-optimal therapeutic response with the current dose or where elevated liver function results suggest a dose reduction is appropriate. Permitted and excluded concomitant medications are defined in the protocol.

**Concomitant Medications**:

PK sampling requirements when F901318 is given concomitantly with either a sensitive CYP3A substrate, a CYP3A inducer, a CYP3A inhibitor or other antifungal medication are detailed in Section 5.9.1.4.

## 6.6 [redacted]

[redacted]

## 6.7 Appropriateness of Measurements

The primary endpoint of overall response is a combined measure of efficacy assessments to evaluate the use of F901318 in the treatment of IFD in patients with no alternative treatment options. It reflects the general clinical approach to the treatment of IFD.

Other assessments, such as measures to evaluate disease progression and all-cause mortality are standard outcome criteria, which are accepted to demonstrate efficacy and treatment response in IFD. In addition, independent assessment of overall response and measurement of drug concentration will support the efficacy and safety analyses.

The EQ-5D-5L is a validated questionnaire to evaluate the effect of treatment on the patients quality of life, and will provide additional insight into the benefit profile of F901318.

# 7.0 QUALITY CONTROL AND QUALITY ASSURANCE

According to the Guidelines of GCP (CPMP/ICH/135/95), the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs). For this study, many of these responsibilities are delegated to a CRO, [redacted].

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meetings
- Central laboratories for analysis of clinical laboratory parameters and plasma levels of F901318 [redacted]
- Central reading of radiological images
- Independent review of safety data by IDSMB
- Independent adjudication of eligibility and response data by a DRC
- Centre Initiation visit
- Early centre visits post-enrolment
- Routine centre monitoring
- Ongoing centre communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final CSR.

Protocol deviations will be identified as soon as possible by the site, the on-site clinical monitor, the MM and the data management team. While every effort should be made to avoid protocol deviations, should a deviation be discovered, Sponsor must be informed. Any protocol deviation impacting Patient safety must be reported to the MM immediately and to the Sponsor.

The Investigator should not implement any deviation from or changes to the protocol without approval by Sponsor and prior review and documented approval/favourable opinion from the IRB of a protocol amendment, except where necessary to eliminate immediate hazards to study

patients, or when the changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change of telephone numbers).

In addition, Sponsor and/or [redacted] Clinical Quality Assurance (CQA) Department may conduct periodic audits of the study processes, including, but not limited to, study centre, centre visits, central laboratories, vendors, clinical database and final CSR. When audits are conducted, access must be authorised for all study-related documents including medical history and concomitant medication documentation to authorised Sponsor's representatives and regulatory authorities.

### 7.1.1 Monitoring

The Sponsor has engaged the services of a CRO, [redacted] to perform all monitoring functions within this clinical study. The monitoring service applies to all study visits, including the ET visits and post-ET FU. [redacted] monitors will work in accordance with [redacted] SOPs and have the same rights and responsibilities as monitors from the Sponsor organisation. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each study centre, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, monitors will check that written informed consent has been obtained from all patients correctly and that data are recorded correctly and completely. Monitors are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. Monitors will also check and ensure adherence to the protocol at the study centre. They will arrange for the supply of investigational product and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted according to all applicable regulatory requirements and standards. Regular monitoring visits will be made to each centre while patients are enrolled in the study. The monitor will make written reports to the Sponsor on each occasion contact with the Investigator is made, regardless of whether it is by phone or in person.

During monitoring visits, all entries in the eCRFs will be compared with the original source documents (source data verification).

### 7.1.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the Data Management and Biostatistics departments [redacted].

Electronic Data Capture will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study centre. Data collection will be completed by authorised study centre staff designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorised study centre staff prior to the study being initiated and any data being entered into the system for any study patients.

All data must be entered in English. The eCRFs should always reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the patient's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study centre staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the eDC application. The appropriate study centre staff will answer queries sent to the Investigator. This will be audit trailed by the eDC application, meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the patient's medical history, that verify the existence of the patient, the inclusion and exclusion criteria and all records covering the patient's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each patient who receives study drug, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All

changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organisation Drug dictionary. Concomitant diseases/medical history will be coded using MedDRA.

### 7.1.3 Quality Assurance Audit

Study centres, the study database and study documentation may be subject to Quality Assurance audit during the course of the study by the Sponsor [redacted] on behalf of F2G. In addition, inspections may be conducted by regulatory bodies at their discretion.

# 8.0 STATISTICS

This is a single-arm open-label, Phase IIb study, and there is no requirement for the Biostatistics Team responsible for the final analysis to be blinded to treatment allocation, nor for a separate, independent Biostatistics Team to provide data on an ongoing basis for IDSMB review.

Data collected in the main study phase up to Day 84/Day 90 and the subsequent 4-week FU visit will be included in the data analyses and presented in the CSR. Data collected during ET will not be included in the data analyses for the CSR, and will be presented in the report addendum.

## 8.1 Determination of Sample Size

This is a single-arm, open-label, Phase IIb study, with no randomization. Four proven invasive fungal infection enrolment categories (disease categories) are defined and there is no upper limit to the enrolment of patients within each culture-proven category. [redacted]. Total enrolment into the study is anticipated to be approximately 200 patients. Given the challenges of recruiting this patient population and the fact that a control arm is not possible in patients with no treatment options, no formal sample size justification is possible. However, it is important to gain as much information as possible to support the treatment of these difficult to treat patients whilst randomized controlled data is also being collected in another trial. [redacted] The efficacy, safety, tolerability and PK of F901318 will be compared in a pre-planned superiority comparison with external control data from the literature and from recent patient databases.

F901318 has been granted Breakthrough Therapy Designation based on preliminary clinical evidence that demonstrates that F901318 may provide substantial improvement over available therapy. As this designation is intended to expedite the development and review of important products, an initial analysis of data will be performed when the first 100 patients have completed treatment to enable the Sponsor to formally consider the possibility that initial approval might be achievable based on these data for the population of patients with limited or no treatment options for life-threatening fungal infections. [redacted]

The efficacy, safety, tolerability and PK of F901318 will be compared with external data generated from a pre-specified plan for matched cases from the [redacted]

## 8.2 Statistical Methods

### 8.2.1 General Considerations

Full details of all analyses and data presentations to be performed will be documented in the Statistical Analysis Plan (SAP). Further, the SAP will include details of the initial analysis and final analysis which will compare the data from this study to the external control data.

Analyses will generally be descriptive in nature with data presented overall and by DRC-adjudicated disease category using appropriate summary statistics. Categorical data will be described using absolute and relative frequencies (n and %). Continuous data will be presented using descriptive statistics (n, mean, standard deviation, minimum, median, and maximum).

Summary statistics will be presented for observed data only. If a Baseline value is missing, no change from Baseline will be calculated. Missing data will be presented as part of a "Missing" category or statistic, if relevant.

Baseline is defined as the last non-missing (scheduled or unscheduled) assessment up to and including Day 1 prior to the first administration of study drug. End of Treatment in the main study phase is defined as the last assessment (scheduled or unscheduled) assigned to treatment, The EOS in the main study for each patient is defined as the last assessment (scheduled or unscheduled) assigned to the study which that patient completes. For patients receiving ET with F901318, EOS and EOT will be the same visit and will occur at approximately Day 90.

Relevant raw and derived variables will be listed in individual by-patient data listings, sorted by DRC-adjudicated disease category, region, centre and patient number.

Data on key endpoints may be summarised separately for the group requiring ET and those who do not require ET. Detail of these presentations will be provided in the SAP.

A sub-group for consideration will be patients receiving extended treatment beyond Day 90. Details on sub-group analyses will be provided in the SAP.

All analyses and data presentation will be performed using SAS® software (Version 9.3 or higher).

Further details of the statistical analysis methods will be provided in the detailed SAP and Tables, Lists and Figures Shells.

### 8.2.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the **DRC-adjudicated overall response** at Day 42 as determined by an independent DRC using a combination of clinical, mycological and radiological results and will be presented overall and by each of the five DRC-adjudicated disease categories as:

- **Success**
- **Failure (where failure includes those patients for whom data at Day 42 cannot be collected or who are considered not evaluable at Day 42)**

The criteria for assessment and categorisation of the DRC-adjudicated overall response will be detailed in the DRC Charter and subsequently specified in the detailed SAP.

Patients withdrawn from study drug due to an unsuccessful overall outcome are required per protocol to return for the main study phase EOT visit but will not be asked to return for the Day 42 and/or Day 84 visits; however, these patients will be considered as failures at all subsequent timepoints.

### 8.2.3 Secondary Efficacy Endpoints

- **DRC-adjudicated overall response (overall and by DRC-adjudicated disease category)** at Day 7, Day 14, Day 28, main study phase EOT, Day 84 and 4-week FU* (as determined by an independent DRC using a combination of clinical, mycological and radiological results) categorised as:
    - **Success**
    - **Failure**

- **Investigator-assessed overall response** (**overall and by DRC-adjudicated disease category** as determined by Investigator using all available assessment results including clinical, mycological and radiologic results) at Day 7, Day 14, Day 28, Day 42, main study phase EOT, Day 84 and 4-week FU* will be categorized as:
    - **Success**
    - **Failure (where failure includes those patients with missing clinical responses or considered not evaluable)**

- **DRC-adjudicated and Investigator-assessed clinical response** overall and by DRC-adjudicated disease category at Day 7, Day 14, Day 28, Day 42, main study phase EOT, Day 84 and 4-week FU* will be categorised as:
    - **Success (categories of Resolution-Complete and Resolution-Partial)**
    - **Failure (categories of Failure-Stable, Failure-Progression, and Results not available)**

- Where appropriate for the IFD, **DRC-adjudicated and Investigator-assessed radiological response** at Day 7, Day 14, Day 28, Day 42, main study phase EOT, Day 84 and 4-week FU*. will be presented overall, by the 5 DRC-adjudicated disease categories and in addition by baseline susceptibility category.

- **DRC-adjudicated and Investigator-assessed mycological response** at Day 7, Day 14, Day

28, Day 42, main study phase EOT, Day 84 and 4-week FU* will be presented overall, by the five DRC-adjudicated disease categories and in addition by baseline susceptibility category based on the categorised response of:

- **Success (Proven or presumed eradication)**
- **Failure (Persistence, presumed persistence, Recurrent or emergent infection or any other response except proven or presumed eradication)**

- **All-cause mortality** rate will be summarised overall and by each of the five DRC-adjudicated disease categories 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 patients who continued therapy beyond Day 90 and who thus have only a single combined main study phase EOT visit encompassing Day 84 and EOT)**.**

*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.

### 8.2.4 Safety Endpoints

Descriptive statistics will be used to present the safety outcomes including:

- Changes in concurrent medication dose and/or frequency resulting from potential DDIs
- Hospitalisations
- Overall exposure, individual dose modification, dose intensity.
- Incidence of treatment-emergent and other (including but not limited to):
  - AEs
  - SAEs (including deaths)
  - AEs leading to death
  - Liver-related AEs
  - AEs leading to premature treatment discontinuation
  - AEs leading to premature study withdrawal
  - AEs by relationship

  - AEs by severity (CTCAE grade)
  - AESIs

- Change from baseline in clinical laboratory test results and incidence of pre-defined treatment-emergent abnormalities (CTCAE)
- Liver-related toxicity: Incidence and time-to-event analyses of elevations in ALT, AST, bilirubin, as described in detail in Section 6.4.2.3.
- Change from baseline in ECG results and incidence of pre-defined treatment-emergent abnormalities (CTCAE)
- Change from baseline in vital signs (including weight and BMI) and incidence of pre-defined treatment-emergent abnormalities (CTCAE)
- [redacted]
- Physical examination: Any abnormal clinically significant findings, as judged by the Investigator, will be listed in a by-patient data listing only.

A treatment-emergent AE (TEAE) is defined as any AE starting or worsening on or after the first dose of study drug up to and including last dose of study drug or during the post-treatment FU. Treatment-emergent AEs which occur in the main study phase or FU will be presented in the study report; TEAEs which occur in the ET phase or post-ET FU will be presented in the report addendum.

### 8.2.5 Pharmacokinetic Analyses

All PK blood sample collections and concentrations from the main study phase will be listed and summarised. Trough samples and post-dose samples will be used for a population PK analysis of F901318. The population PK analysis will be performed in accordance with a separate modelling data analysis plan and reported outside of the CSR.

Parameters for the Intensive PK analysis set will be determined using non-compartmental analysis. All PK parameters will be listed and summarised using appropriate descriptive statistics.

The PK data from samples collected during the extended treatment phase will be presented in the report addendum.

### 8.2.6 Data to be Analysed

Data handling and statistical analysis will be the responsibility of [redacted]. The data will be inspected for inconsistencies by performing validation checks.

All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the SAP prepared by [redacted] and authorised by F2G prior to database lock.

### 8.2.7 Analysis Sets

The different analysis sets to be used in this study are described below:

- All Patients Enrolled analysis set: all patients who provide written informed consent.
- Safety analysis set (SAF): all patients who receive at least one dose of study drug (or part thereof). The SAF will be used for the analysis of all safety data.
- Intent-to-treat (ITT) population: all patients who receive at least one dose of study drug.
- Modified Intent-to-treat (mITT) population: all patients who receive at least one dose of study drug and who are assigned to a DRC-adjudicated disease category. The mITT population and sub-populations based on DRC-adjudicated disease categories will be used for the analysis of efficacy data.
- Trough PK analysis set (Trough PK set): all patients who received at least one dose of study drug and have at least one measured trough F901318 plasma concentration.
- Intensive PK analysis set (Intensive PK set): a subset of the SAF population who have [redacted]. Further details on sub-categories (dose level and concomitant medication dependent) will be provided in the modelling analysis plan.

### 8.2.8 Missing Data

Data from patients who withdraw from the study, including AEs and any follow-up, will be included in the analyses of primary and secondary outcomes as relevant. Further details will be provided in the SAP.

## 8.3 Patient Disposition

The number of patients enrolled, completed or prematurely withdrawn from study participation together with the primary reason for premature study withdrawal will be presented overall and by DRC-adjudicated disease category, for each region, centre, as relevant, and overall, using absolute and relative frequencies (n and %).

Similarly, the number of patients enrolled, treated, completed or prematurely discontinued treatment together with the primary reason for premature treatment discontinuation will be summarised.

The decision to exclude patients from any of the analysis sets will be finalised at a data review meeting with F2G prior to final database lock. Such patients will be listed and a summary of the main reason(s) for exclusion will be provided.

The number of patients included in each analysis set will be summarised. Reason(s) for exclusion can be protocol deviations or other factors that may affect the efficacy outcome or treatment of the patient.

Major/critical protocol deviations as collected during the conduct of the study and as authorised prior to final database lock will be summarised in a similar manner and listed per patient, describing the nature of the deviation.

## 8.4 Patient Characteristics

Patient characteristics may include, but are not limited to: age, gender, race/ethnicity, height, weight, and BMI. Patient characteristics will be summarised for observed data only, overall and by DRC-adjudicated disease category, using descriptive statistics for continuous variables (sample size [n], mean, standard deviation, median, minimum, and maximum) and for categorical variables (sample size [n], absolute and relative frequencies [n and %]). Missing data will be included as part of a missing category or statistic as relevant.

## 8.5 Disease Characteristics

Disease characteristics of the underlying infection (IFD) will be listed and summarised in a similar manner as described above and may include (but not limited to):

- Duration from initial diagnosis to first administration of study drug.
- Diagnostic method
- Causative organism (in the event a patient has multiple organisms, information for all relevant organisms will be listed)
- Treatment regimen and response to previous treatment

In addition, history of all other fungal, viral and bacterial infections within the 6-month period prior to first administration of study drug will be presented.

## 8.6 Medical History

Medical history will be presented by MedDRA System Organ Class and Preferred Term using the most recent version of MedDRA.

## 8.7 Medications and Procedures

With reference to Section 6.2.6 and Section 6.2.7, medications and procedures will be categorised based on dates of administration/occurrence as either prior, concomitant or post-treatment. Medications will be coded using the World Health Organisation Drug Dictionary and presented overall and by DRC-adjudicated disease category, by Anatomical Therapeutic Chemical class and Preferred Term.

## 8.8 Efficacy Analyses

In addition to the below, efficacy data will be summarised descriptively, overall and by DRC-adjudicated disease category. If deemed relevant, summary statistics may be presented by relevant subgroups considered to impact the efficacy outcome. Efficacy data collected for the main study phase up to Day 84/Day 90 and the subsequent 4-week FU visit will be included in the data analyses and presented in the CSR. [redacted]

### 8.8.1 Primary Efficacy Analysis

With reference to Section 8.2.2, based on the DRC-adjudicated overall response categorized as success or failure a response rate will be calculated based on all patients included in the mITT population where missing clinical responses or patients considered not evaluable at Day 42 will be included as a failure. A 95% CI for the single binomial proportion will be calculated. [redacted]

Corresponding estimated historical response rates in relevant control populations will be assessed using analyses of available clinical databases [redacted] and presented in a similar manner as the calculated Study 32 response rate.

### 8.8.2 Secondary Efficacy Analyses

With reference to Section 8.2.3 and based on definitions in Section 6.3 and the DRC Charter**:**

**DRC-adjudicated overall response at Day 7, Day 14, Day 28, main study phase EOT, Day 84 and 4-week FU* (as determined by an independent DRC using a combination of clinical, mycological and radiological results)**

Results for DRC-adjudicated overall response at Day 7, Day 14, Day 28, main study phase EOT, Day 84 and 4-week FU will be presented in a similar manner as described for the primary efficacy analysis.

**Investigator-assessed overall response (as determined by Investigator using combined clinical, mycological and radiological results) at Day 7, Day 14, Day 28, Day 42, main study phase EOT, Day 84 and 4-week FU***

Based on the Investigator-assessed overall response categorised as success/failure, a response rate will be calculated based on all patients included in the mITT population where patients considered not evaluable at Day 42 due to missing data will be included as failures. In addition a 95% CI for a single binomial proportion will be calculated. The 95% CI of this response rate will be compared with an estimated historical response rate, overall and by DRC-adjudicated disease category.

**DRC-adjudicated and Investigator-assessed clinical response overall and by DRC-adjudicated disease category at Day 7, Day 14, Day 28, Day 42, main study phase EOT, Day 84 and 4-week FU***

Based on the DRC-adjudicated and Investigator-assessed clinical response categorised as success/failure, a response rate will be calculated based on all patients included in the mITT population where patients considered not evaluable due to missing clinical data will be included as failures. In addition a 95% CI for a single binomial proportion will be calculated.

**DRC-adjudicated and Investigator-assessed mycological response overall and by DRC-adjudicated disease category at Day 7, Day 14, Day 28, Day 42, main study phase EOT, Day 84 and 4-week FU***

Based on the DRC-adjudicated and Investigator-assessed mycological response categorized as Success/Failure, a response rate will be calculated based on all patients included in the mITT population with a baseline culture result available. Patients with a mycology evaluation of "No mycological Follow-up results available" will be assigned an outcome of presumed eradication if they are deemed a clinical success and a presumed failure if they are deemed a clinical failure, or clinical response is missing. Mycological success will include patients classified as a success or a presumed eradication. In addition a 95% CI for a single binomial proportion will be calculated.

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

Mortality rates will be derived at Day 42, main study phase EOT, Day 84 and 4-week FU* based on all patients in the mITT population. In addition a 95% CI for a single binomial proportion will be calculated. Also, Kaplan-Meier analyses will be performed at Day 42, main study phase EOT, Day 84 and 4-week FU*, summarising median time to death (stratified by DRC-adjudicated disease category). A reported death will be carried forward for all future visits. A patient without reported death for the specific visit analysed (Day 42, main study phase EOT, Day 84 or 4-week FU*) will be censored for the specific visit analysed.

**Note: 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. As judged relevant, subanalyses will be performed to account for this difference in observation periods.*

### 8.8.3 Patient-Reported Outcomes

The EQ-5D-5L qualitative items will be presented as the number and % of patients with each rating of health for each quality of life category (such as mobility), summarised over all

scheduled visits. The number and % of patients with each shift item from baseline to EOT and from baseline to EOS will also be summarized.

The EQ-5D-5L qualitative items will be presented by means of a stacked bar chart over all applicable scheduled visits.

Descriptive statistics will be summarized for the visual analogue scale score.

## 8.9 Safety

Frequency tables will be used to present the safety outcomes including incidences of TEAEs, SAEs (including deaths), TEAEs leading to death, treatment-emergent AESIs, liver-related TEAEs, TEAEs leading to premature treatment discontinuation, TEAEs leading to premature study withdrawal, TEAEs by relationship and TEAEs by severity.

Change from baseline and incidence of pre-defined treatment-emergent newly occurring abnormalities in vital signs, clinical laboratory test results and ECG results will be summarised. Graphical presentations will also be used to help describe vital signs, selected laboratory test values and ECG parameters.

Other safety outcomes include physical examination [redacted]

Safety data collected for the main study phase up to Day 84/Day 90 and the subsequent 4-week FU visit will be included in the data analyses and presented in the CSR. Safety data collected during ET and ET FU will not be included in the data analyses or in the CSR, and will be presented in the report addendum.

### 8.9.1 Exposure

Overall exposure will be summarised by taking individual dose modification and dose intensity into account.

### 8.9.2 Adverse Events

Adverse events will be coded using MedDRA. Number of events and incidence rates will be tabulated by System Organ Class and Preferred Term. An event that occurs at least once on the date of, or subsequent to first administration of study drug will contribute one observation to the numerator of the incidence rate. The denominator of the rate will comprise all patients exposed to the study drug (SAF analysis set). If the intensity or seriousness of the AE changes, the overall severity or seriousness will be the worst severity or seriousness of the multiple occurrences.

TEAEs, SAEs (including deaths), TEAEs leading to death, treatment-emergent AESIs, liver-related TEAEs, TEAEs leading to premature treatment discontinuation and TEAEs leading to premature study withdrawal will be tabulated. In addition, TEAEs by relationship and severity (using CTCAE grading) will be summarised.

### 8.9.3 Clinical Laboratory Evaluations

All central laboratory test results will be summarised using descriptive statistics at each visit for observed data and change from baseline.

Based on the laboratory reference range, laboratory test results will be categorised as:

- Low
- Normal
- High

Change from baseline to each post-baseline visit, main study phase EOT and EOS in aforementioned reference range laboratory category will be presented as shift tables. Abnormal laboratory values, categorised per reference range as high or low will be flagged in by-patient data listings.

In addition, pre-defined treatment-emergent abnormalities (newly occurring), as defined by CTCAE criteria, will be presented in tables where the incidence rate will be based on the total number of patients 'at risk':

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post-dose value recorded.

In the event that a laboratory value does not comply with the CTCAE criterion, the laboratory value will be categorised as normal.

In the event of a retest of the same sample due to, for example, a laboratory error (same visit number assigned), the last available assessment will be used for by-visit summaries, including identification of pre-defined treatment-emergent abnormalities (newly occurring), regardless of whether the laboratory assessment for that particular nominal visit is available or not.

The handling of laboratory values below limit of quantification (LOQ) will be described in the detailed SAP for each laboratory test separately.

It should be noted that for glucose, only non-fasting values will be included in any summary presentations although all results will be listed in by-patient listings.

As per the FDA Liver Safety Guidance, the following treatment-emergent incidence tables will be presented, including time-to-event analyses, and by-patient data listings:

- 3 ×-, 5 ×-, 10 ×-, and 20 × ULN elevations of AST, ALT, and either ALT or AST.
- Any elevations of total bilirubin, elevated total bilirubin > 2 × ULN.
- Any elevations of alkaline phosphatase (ALP) > 1.5 × ULN.

- Elevation of AST or ALT > 3 × ULN accompanied by elevated total bilirubin (> 1.5 × ULN, > 2 × ULN).
- Elevation of AST or ALT > 3 × ULN in temporal association with nausea, vomiting, anorexia, abdominal pain, or fatigue.

Treatment-emergent is defined as any event (scheduled or unscheduled) which started or worsened on or after the first dose of study drug or during the post-treatment FU. Treatment-emergent AEs which occur in the main study phase or FU will be presented in the study report; TEAEs which occur in the ET phase or post-ET FU will be presented in the report addendum.

In addition, figures and listings will be presented for possible treatment-emergent Hy's Law cases (patients with any elevated AST or ALT > 3 × ULN, ALP < 2 × ULN and associated with an increase in total bilirubin ≥ 2 × ULN).

[redacted]

### 8.9.4 Vital Signs Measurements, ECG, Physical Findings and Other Safety Evaluations

#### 8.9.4.1 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature, weight and BMI) will be summarised using descriptive statistics at each visit for observed data and change from baseline.

Pre-defined treatment-emergent abnormalities (newly occurring), as defined by CTCAE criteria, will be presented in tables and listed, where the incidence rate will be based on the total number of patients 'at risk' (see example in Section 8.9.3).

A similar approach as for laboratory values will be followed for vital signs with regards to retests and values not complying with CTCAE criterion.

#### 8.9.4.2 ECG

ECG results will be summarised using descriptive statistics at each visit for observed data and change from baseline.

Pre-defined QT interval treatment-emergent abnormalities, as defined by CTCAE criteria, will be presented in tables and listed, where the incidence rate will be based on the total number of patients 'at risk' (see example in Section 8.9.3).

A similar approach as for laboratory values will be followed for ECG with regards to retests and values not complying with CTCAE criterion.

Change from baseline to each post-baseline visit, main study phase EOT and EOS in Investigator-judged abnormal classification will be presented as shift tables:

- Abnormal and clinically significant
- Abnormal and not clinically significant
- Normal.

#### 8.9.4.3 Other Safety Evaluations

Any abnormal physical examination findings, as judged by the Investigator, will be listed in a by-patient data listing only.

[redacted]

Any abnormal physical examination findings, as judged by the Investigator, will be listed in a by-patient data listing only.

## 8.10 Hospitalisation Status

The reason, date of admission and discharge, type of ward (intensive care unit, non-intensive care unit) and any changes in any of these parameters recorded in the eCRF will be summarised descriptively (sample size [n], absolute and relative frequencies [n and %]).

## 8.11 Pharmacokinetic Analyses

Blood samples for analysis of plasma concentrations of study drug will be collected as specified in the Schedule of Events (Table 1).

[redacted]

All PK sample collections and concentrations will be listed and summarised by visit. Pharmacokinetic data collected for the main study phase up to Day 84/Day 90 and the subsequent 4-week FU visit will be included in the data analyses and presented in the CSR. Pharmacokinetic data collected during ET and ET FU will not be included in the data analyses or in the CSR, and will be presented in the report addendum.

### 8.11.1 Trough Sampling Data Analysis

All drug concentrations will be listed and presented in tabular summaries using descriptive statistics, including n, arithmetic mean, standard deviation, coefficient of variation, median, geometric mean, geometric coefficient of variation, minimum and maximum values.

The trough concentrations and post-dose concentrations will be used for a population PK analysis of F901318. The population PK of F901318 will be characterised by nonlinear mixed-effects modelling. From this analysis, the influence of various demographic covariates (e.g., body weight, gender) and other patient-specific factors on F901318 trough levels and drug exposure may be assessed. Correlations between exposure and response or safety data will be evaluated as appropriate.

The data from this study may be combined with data collected from other studies and from the Intensive PK component of this study to supplement model development. The population PK analysis will be performed in accordance with a separate modelling data analysis plan and may be reported outside of the CSR.

### 8.11.2 Intensive PK Data Analysis

The Intensive PK study will include densely sampled PK to allow parameters to be determined using standard noncompartmental analysis. All PK parameters where possible to estimate will be listed and summarised using appropriate descriptive statistics including maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($t_{max}$), area under the curve over the 12 hour dosing interval ($AUC_{tau}$), trough concentration 12 hours post-dose ($C_{min}$), apparent clearance (CL/F) and apparent volume of distribution ($V_z$/F). Data will be listed and summarised using n, arithmetic mean, standard deviation, coefficient of variation, median, minimum and maximum values. Geometric mean and geometric coefficient of variation will also be included for any PK parameter calculations, except for $t_{max}$ which will be summarised using n, minimum, median and maximum only. Full details of the analysis will be provided in the SAP supporting this clinical study.

## 8.12 [redacted]

[redacted]

## 8.13 Interim Analyses

An analysis of the data will be conducted when the first 100 patients have completed the main study phase.

Independent Data and Safety Monitoring Board (IDSMB)

See Section 6.4.4.1 for details.

Data Review Committee (DRC)

A DRC will be established to conduct a review of all patient cases to determine diagnosis and overall outcome. Members of the DRC will be independent from the Sponsor and also will not participate as Investigators in the study. The DRC will consist of experts in the field of clinical mycology.

The DRC assessment will include the clinical diagnosis at enrolment as well as primary and secondary criteria for efficacy evaluation. The DRC will not review data from the ET visits or the post-ET FU. Objectives, composition, process and documentation of the DRC are described in more detail in the DRC Charter and SAP.

# 9.0 ETHICS

## 9.1 Institutional Review Board or Independent Ethics Committee

An Ethics Committee should approve the final protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will provide the Sponsor [redacted] with documentation of IRB/IEC approval of the protocol and informed consent before the study may begin at the study centre(s). The Investigator should submit the written approval to F2G or representative before enrolment of any patient into the study.

F2G or representative should approve any modifications to the ICF that are needed to meet local requirements.

The Investigator will supply documentation to the Sponsor [redacted] of required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of patients or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the study, the Investigator will provide the ethics committee with a brief report of the outcome of the study, if required.

F2G [redacted] will provide Regulatory Authorities, Ethics Committees and Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions, where relevant.

Each Investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the study drug. F2G or [redacted] will provide this information to the Investigator so that he/she can meet these reporting requirements.

## 9.2 Ethical Conduct of the Study

This study will be conducted and the informed consent will be obtained in accordance with the ICH GCP guidelines, the European Union Clinical Trials Directive 2001/20/EC, the provisions of the Helsinki Declaration, and relevant legislation in force in the countries where the study will be conducted.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human patients. The study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety and well-being of the participating study patients

are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

## 9.3 Patient Information and Informed Consent

The ICF will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient will be entered into the study. The ICF contains a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time. Written consent must be given by the patient and/or legal representative (if applicable and conforming with local regulations), after the receipt of detailed information on the study. A separate written consent must be given by the patient and/or legal representative if the patient is to receive ET beyond Day 84/90.

The Investigator is responsible for ensuring that informed consent is obtained from each patient or legal representative and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug. The Investigator will provide each patient with a copy of the signed and dated consent form.

## 9.4 Patient Data Protection

[redacted]

# 10.0 STUDY ADMINISTRATION

## 10.1 Administrative Structure

This study will be outsourced, and the Sponsor has engaged [redacted] a CRO, to oversee the clinical conduct of this study, including project management and monitoring.

The Sponsor and [redacted] may also engage other third-party providers as necessary.

## 10.2 Data Handling and Record Keeping

It is the Investigator's responsibility to maintain essential study documents (protocol and protocol amendments, completed eCRFs, signed ICFs, relevant correspondence and all other supporting documentation). The study centre should plan on retaining such documents for approximately 15 years after study completion. The study centre should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the study is being conducted. Patient identification codes (patient names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the Sponsor, who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records.

For studies conducted outside the United States under a US IND, the Principal Investigator must comply with US FDA IND regulations and with those of the relevant national and local health authorities.

## 10.3 Direct Access to Source Data/Documents

The Investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each patient enrolled into the study.

The Investigator will allow the Sponsor, [redacted], and authorized regulatory authorities to have direct access to all documents pertaining to the study, including individual patient medical records, as appropriate.

## 10.4 Investigator Information

### 10.4.1 Investigator Obligations

This study will be conducted in accordance with the ICH Harmonized Tripartite Guideline for GCP (GCP, 1997; the US CFR Title 21 parts 50, 56, and 312; and European Legislation) and the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator will agree to conduct the clinical study in compliance with this protocol after the approval of the protocol by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

### 10.4.2 Protocol Signatures

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 1). By signing the protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol and will conduct the study in accordance with ICH Tripartite Guidelines for Good Clinical Practice and applicable regulatory requirements. The study will not be able to start at any centre where the Investigator has not signed the protocol.

### 10.4.3 Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study centre will be set forth in the Clinical Trial Agreement.

## 10.5 Financing and Insurance

The Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the patients participating in this study. The terms of the insurance will be kept in the study files.

# 11.0 REFERENCES

Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: An international consensus. Clinical Infectious Diseases. 2002;34(1):7-14.

Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934 26: 404–413. doi:10.1093/biomet/26.4.404

Cortez KJ, Roilides E, Quiroz-Telles F, Meletiadis J, Antachopoulos C, Knudsen T, et al. Infections caused by Scedosporium spp. Clin Microbiol Rev. 2008;21(1):157-97,CP3.

CredibleMeds® Combined list of drugs that prolong QT and/or cause Torsades de Pointes (TDP). Arizona Center for Education and Research on Therapeutics. Available at: https://www.crediblemeds.org/pdftemp/pdf/CombinedList.pdf

De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clinical Infectious Diseases. 2008;46(12):1813-21.

Denning DW. Invasive aspergillosis. Clinical Infectious Diseases. 1998;26(4):781-803.

Denning DW. Therapeutic outcome in invasive aspergillosis. Clinical Infectious Diseases. 1996;23:608-15.

Dixon C. Statistical Review from 22 Jan 2015 FDA AIDAC review of isavuconazonium (transcript page 123). 2015.

European Center for Disease Prevention and Control. ECDC Technical Report: Risk assessment on the impact of environmental usage of triazoles on the development and spread of resistance to medical triazoles in Aspergillus species. Accessed 23 Mar 2015 at http://ecdceuropaeu/en/publications/Publications/risk-assessment-impact-environmental-usage-of-triazoles-on-Aspergillus-spp-resistance-to-medical-triazolespdf. 2013.

FDA guidance on drug-drug interactions, accessed online at https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Garcia-Rubio R, Cuenca-Estrella M, Mellado E. Triazole Resistance in Aspergillus Species: An Emerging Problem. Drugs. 2017;77(6):599-613.

Guo-Hao Xie, Xiang-Ming Fang, Qiang Fang, Xin-Min Wu, Yu-Hong Jin, Jun-Lu Wang et al. Impact of invasive fungal infection on outcomes of severe sepsis: a multicenter matched cohort study in critically ill surgical patients. Critical Care 2008, 12:R5

Heath CH, Slavin MA, Sorrell TC, Handke R, Harun A, Phillips M, et al. Population-based surveillance for scedosporiosis in Australia: epidemiology, disease manifestations and emergence of Scedosporium aurantiacum infection. Clin Microbiol Infect. 2009;15(7):689-93.

Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347(6):408-15.

Kelly M, Stevens R, Konecny P. Lomentospora prolificans endocarditis--case report and literature review. BMC Infect Dis. 2016;16:36.

Kennedy B, Larcombe R, Chaptini C, Gordon DL. Interaction between voriconazole and flucloxacillin during treatment of disseminated Scedosporium apiospermum infection. The Journal of antimicrobial chemotherapy. 2015;70(7):2171-3.

Lamoth F, Chung SJ, Damonti L, Alexander BD. Changing Epidemiology of Invasive Mold Infections in Patients Receiving Azole Prophylaxis. Clinical Infectious Diseases. 2017;64(11):1619-21.

Lamoth F. Aspergillus fumigatus-Related Species in Clinical Practice. Frontiers in microbiology. 2016;7:683.

Maertens JA, Raad, II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): A Phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387(10020):760-9.

Magill S, Chiller T and Warnock D. Evolving strategies in the management of aspergillosis. Expert Opin. Pharmacother. 2008;9:193-209

Muilwijk EW, Dekkers BGJ, Henriet SSV, Verweij PE, Witjes B, Lashof A, et al. Flucloxacillin Results in Suboptimal Plasma Voriconazole Concentrations. Antimicrobial agents and chemotherapy. 2017;61(9).

Nivoix Y, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Amé S, Fohrer C, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. Clin Infect Dis. 2008;47:1176-84

Rodriguez-Tudela JL, Berenguer J, Guarro J, Kantarcioglu AS, Horre R, De Hoog GS, et al. Epidemiology and outcome of Scedosporium prolificans infection, a review of 162 cases. Med Mycol. 2009;47(4):359-70. Steinmann J, Hamprecht A, Vehreschild MJ, Cornely OA, Buchheidt D, Spiess B, et al. Emergence of azole-resistant invasive aspergillosis in HSCT recipients in Germany. The Journal of antimicrobial chemotherapy. 2015;70(5):1522-6.

Tammer I, Tintelnot K, Braun-Dullaeus RC, Mawrin C, Scherlach C, Schluter D, et al. Infections due to Pseudallescheria/Scedosporium species in patients with advanced HIV disease--a diagnostic and therapeutic challenge. Int J Infect Dis. 2011;15(6):e422-9.

Tortorano AM, Richardson M, Roilides E, van Diepeningen A, Caira M, Munoz P, et al. ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: Fusarium spp., Scedosporium spp. and others. Clin Microbiol Infect. 2014;20 Suppl 3:27-46.

van der Linden JW, Snelders E, Kampinga GA, Rijnders BJ, Mattsson E, Debets-Ossenkopp YJ, et al. Clinical implications of azole resistance in Aspergillus fumigatus, The Netherlands, 2007-2009. Emerg Infect Dis. 2011;17(10):1846-54.

Verweij PE, Chowdhary A, Melchers WJ, Meis JF. Azole Resistance in Aspergillus fumigatus: Can We Retain the Clinical Use of Mold-Active Antifungal Azoles? Clinical Infectious Diseases. 2016;62(3):362-8.

Verweij PE, Donnelly JP, Kullberg BJ, Meis JFGM, De Pauw BE. Amphotericin B versus amphotericin B plus 5-flucytosine: Poor results in the treatment of proven systemic mycoses in neutropenic patients. Infection. 1994;22:81-5.

# 12.0 APPENDICES

# APPENDIX 1: SIGNATURE OF INVESTIGATOR

**PROTOCOL TITLE:** 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.

**PROTOCOL NO:** F901318/0032

This protocol is a confidential communication of F2G. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from F2G.

| |
|---|
| Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the centre in which the study will be conducted. Return the signed copy to IQVIA. |

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Centre: _____

_____

_____

# APPENDIX 2: DEFINITIONS OF INVASIVE FUNGAL DISEASE (IFD) AND DIAGNOSTIC CRITERIA IN REFERENCE TO EORTC MSG (DE PAUW 2008)

## Definitions of IFD:

**Proven Invasive Fungal Disease (MOULDS)**

| Analysis and Specimen | Moulds |
|---|---|
| **Microscopic Analysis (sterile material)** | Histopathologic, cytopathologic, or direct microscopic examination[a] of a specimen obtained by needle aspiration or biopsy in which hyphae or melanized yeast-like forms are seen accompanied by evidence of associated tissue damage *(microscopically or as an infiltrate or lesion by imaging)* **OR** |
| **Culture (sterile material)** | Recovery of a mould or "black yeast" by culture of a specimen obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with an infectious disease process (e.g. transbronchial biopsy, open-lung biopsy, or brain biopsy), excluding bronchoalveolar lavage (BAL) fluid, a cranial sinus cavity specimen, and urine |
| **Blood** | Blood culture that yields a mould[b] (e.g. Fusarium species) in the context of a compatible infectious disease process |
| **Serological analysis: CSF** | Not applicable |

**a.** Tissue and cells submitted for histopathologic or cytopathologic studies should be stained by Grocott-Gomorri methenamine silver stain or by periodic acid Schiff stain, to facilitate inspection of fungal structures. Whenever possible, wet mounts of specimens from foci related to invasive fungal disease should be stained with a fluorescent dye (e.g. calcofluor or blankophor).

**b.** Recovery of *Aspergillus* species from blood cultures invariably represents contamination

**Probable Invasive Fungal Disease - Lower Respiratory Tract Disease Invasive Aspergillosis (LRTD IA)**

At least one high-risk host factor (definitions see below)

PLUS, at least one clinical feature (definitions see below)

PLUS, at least one mycological criterion (definitions, see below)

***Host factors and clinical features are not required for patients with Proven IFD. However, if such host factors and clinical features are present at baseline, they will be recorded in the eCRF.***

## Definitions of Diagnostic Criteria:

**Host Factors:**

- Recently resolved (< *4 weeks*) or ongoing neutropenia (neutropenia defined as absolute neutrophil count < $0.5 \times 10^9$ cells/L [< 500 cells/$mm^3$] for ≥ 10 days), temporally related to the onset of fungal disease.
- Receipt of an allogeneic haematopoietic stem cell transplant (HSCT) or bone marrow transplant (BMT).
- Prolonged use of corticosteroids (excluding among patients with allergic bronchopulmonary aspergillosis) at a mean minimum dose of 0.3 mg/kg/day of prednisone equivalent for > 3 weeks.
- Treatment with other recognized T-cell immunosuppressants, such as cyclosporine, tacrolimus, monoclonal antibodies or nucleoside analogues during the past 90 days.
- Inherited severe immunodeficiency (such as chronic granulomatous disease or severe combined immunodeficiency).

**Clinical Features:**
**Lower Respiratory Tract Fungal Disease**

*The medical history must be established to exclude alternative aetiologies and to distinguish between an acute or subacute presentation rather than a chronic pulmonary infection. Onset of clinical symptoms and/or physical findings within approximately 2 weeks prior to the first administration of study drug defines an acute or subacute pulmonary infection.*

The presence of **at least one** of the following **"specific" imaging signs on computed tomography (CT), high resolution computed tomography (HRCT) or magnetic resonance imaging (MRI)**:

i. Dense well-circumscribed lesion(s) (nodules) with or without halo sign
ii. Air crescent sign
iii. Cavity
iv. Wedge-shaped and segmental or lobar consolidation*****
v. Reverse halo sign*****

***** *Planned updates for 2019 EORTC Guideline Revision and will be considered by the MM for study inclusion if applicable.*

**OR**

Allogeneic HSCT/BMT or neutropenic patients who have non-specific focal infiltrates, on CT scan (or HRCT) or MRI, must have mycological evidence of disease at the time of study entry and will be classified as probable. Otherwise, patients with non-specific focal infiltrates are not eligible.

The presence of other clinical findings (pleural rub, pleural pain, or haemoptysis) will be recorded but these features are not thought sufficiently predictive to be used alone.

**Non Lower Respiratory Tract Fungal Disease**

Probable LRTD IA is the only unconfirmed IFD eligible for this study. Radiology response will be assessed for any proven Non-LRTD IFD patients enrolled in the study.

The Clinical features for Non-LRTD are as follows -

**Tracheobronchitis**

Tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar seen on bronchoscopic analysis

**Sinonasal infection**

Imaging showing sinusitis plus at least 1 of the following 3 signs:

i. Acute localized pain (including pain radiating to the eye)
ii. Nasal ulcer with black eschar
iii. Extension from the paranasal sinus across bony barriers, including into the orbit

**CNS infection**

Imaging showing 1 of the following 2 signs:

i. Focal lesions on imaging
ii. Meningeal enhancement on MRI or CT

**Mycological Criteria:**

Evidence may include cytology, direct microscopy, culture from non-sterile sites, antigen detection and polymerase chain reaction (PCR).

For Proven IFD patients the following will be not be sufficient to enrol the patient into the study BUT the results of any mycological assessments (PCR, GM, β-D-glucan etc.) from non sterile sites will be documented in the eCRF.

For the Probable LRTD IA Patients they must meet ONE of the following criteria:

Direct test (cytology, direct microscopy, or culture)

Either sputum, BAL, bronchial brush samples, or sinus aspirate specimen demonstrating the presence of fungal elements either by recovery by culture of a mould or detection by cytology or direct microscopy of hyphal forms

**OR**

Indirect tests (detection of antigen or cell wall constituents)

Serum galactomannan (GM) with a single value of ≥1.0 or two consecutive values each of ≥0.5 (i.e., from 2 separate blood draws) is acceptable mycological evidence for enrolment as probable IFD. Patients with serum GM meeting the protocol-defined requirements drawn within 10 days prior to first dose of study drug are eligible for enrolment. Patients receiving concomitant amoxicillin/clavulanate, piperacillin/tazobactam or Plasma-Lyte™ (Baxter) should be discussed with the Medical Monitor, and these products must be recorded in the prior and/or concomitant medication pages of the eCRF.

Bronchoalveolar lavage fluid: GM index ≥1.0 from testing of two aliquots of a single BAL fluid sample is acceptable as mycological evidence for enrolment as probable IFD.

**Note:** GM results from other specimens are not acceptable evidence of probable IA but results will be reported in the eCRF.

Positive *Aspergillus* PCR result from blood in two separate specimens, performed locally and/or centrally. The elected PCR assay and process methodology should be in accordance with latest EORTC/MSG recommendations.

**Note:** Aspergillus PCR from other fluids is not acceptable as evidence.

**Proven endemic mycosis:**

In a patient with an illness consistent with an endemic mycosis, a history of one of the following:

i. Recovery in culture from a specimen obtained from the affected site or from blood
ii. Histopathologic or direct microscopic demonstration of appropriate morphologic forms with a truly distinctive appearance characteristic of dimorphic fungi, such as Coccidioidesspecies spherules, Blastomyces dermatitidis thick-walled broad-based budding yeasts, Paracoccidioides brasiliensis multiple budding yeast cells, and, in the case of histoplasmosis, the presence of characteristic intracellular yeast forms in a phagocyte in a peripheral blood smear or in tissue macrophages
iii. For coccidioidomycosis, demonstration of coccidioidal antibody in CSF, or a 2-fold rise in 2 consecutive serum samples with abnormal CSF findings indicative of coccidioidomycosis
iv. For paracoccidioidomycosis, demonstration in 2 consecutive serum samples of a precipitin band to paracoccidioidin concurrently in the setting of an ongoing infectious disease process.

# APPENDIX 3: LIVER BIOCHEMISTRY MANAGEMENT ALGORITHM

**The Liver Biochemistry Management Algorithm must be applied in the Main Study Phase and in the Extended Treatment Phase.**

**Per Table 1 (Summary of Assessments), at screening:** Full Liver Panel (see definitions, below)

**Per Table 1 (Summary of Assessments) and Table 3 (extended treatment), after enrolment:**

[redacted]

[1] Stopping rules adapted from rules suggested in *US FDA. Guidance for industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. March 2009.*

[redacted]

**Safety Reporting**

1) Moderate and Major Enzyme Elevations:
   a) Must be reported as an AESI; see also Section 6.4.1
   b) Should be reported as an SAE if the seriousness criteria are met; see also Section 6.4.1
   c) Must be reported as a medically significant SAE, regardless of causality, if the enzyme elevations are either ALT/AST > 3x ULN with total bilirubin > 2x ULN or ALT/AST> 20 x ULN
   d) Should receive expedited follow-up reporting and review by the Sponsor
   e) Will be reviewed by a Sponsor-organized independent hepatic review process

**Definition of Basic Liver panel:** AST, ALT, GGT, alkaline phosphatase, bilirubin (total and direct), and albumin

**Definition of Full Liver panel:** Basic Liver Panel plus PT and aPTT

**Definition of <u>Major Enzyme Elevation</u> from baseline**
1) ALT or AST > 10x ULN *or*
2) ALT or AST > 2x baseline (if baseline was > 1.5x ULN) or > 3x ULN (if baseline was ≤ 1.5x ULN) <u>AND</u>
   a) Total Bilirubin > 1.5x baseline (or > 1.5xULN if baseline was ≤ ULN) *or*
   b) There are new and otherwise unexplained clinical findings potentially referable to the liver: nausea, jaundice, right upper abdominal pain, fever, or rash

**Definition of <u>Moderate Enzyme Elevation</u> from baseline**
1) ALT or AST > 2x baseline (if baseline was > 1.5x ULN) or > 3x ULN (if baseline was ≤ 1.5x ULN)*

[redacted]

# APPENDIX 4: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

### Document History

| Document | Date | Substantial | Region |
|---|---|---|---|
| Amendment 06 | 28 February 2020 | Yes | Global |
| Amendment 05 | 30 October 2019 | Yes | Global (not implemented) |
| Amendment 04 | 03 May 2019 | Yes | Global |
| Amendment 03 | 28 November 2018 | Yes | Global |
| Amendment 02 | 02 May 2018 | Yes | Global |
| Amendment 01-01 | 07 March 2018 | Yes | Local (Belgium) |
| Amendment 01 | 24 January 2018 | Yes | Global |
| Original Protocol | 19 December 2017 | - | - |

### Amendment 05 30 October 2019

Amendment 05 was not implemented. Changes introduced to Amendment 05 which are relevant to Amendment 06 are included in the Summary of Changes for Amendment 06.

### Amendment 04 03 May 2019

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

### Overall Rationale for Amendment 04

An extended treatment phase has been added to the study to allow continued treatment with F901318 for those patients who have benefitted from treatment with F901318 during the 90 day study treatment period, have no suitable alternative treatment options and would continue to benefit from extended treatment. In prior versions of this protocol, extended treatment has been provided via a Named Patient mechanism in each territory. As is standard with Named Patient mechanisms, the ability of the Sponsor to closely follow and support patients is limited and the data from patients utilizing this mechanism is not incorporated into study reports. As it has become clear that extended treatment is being found beneficial in approximately 25% of enrolled patients, Amendment 04 provides an explicit mechanism for this process that will allow the data from these patients to ultimately be provided as an addendum to the primary report for this study.

Extended treatment is to be requested by the Investigator and must be approved by the Medical Monitor. Patients will attend visits every 4 weeks during extended treatment to assess the safety

of continued treatment and to confirm by the evaluation of efficacy that continued treatment is justified. Assessment of the safety and efficacy of F901318 during extended treatment has been added as an exploratory objective. Detail has been presented of the assessments and procedures to be completed during extended treatment.

Patient-reported outcomes have been added as an endpoint, to be collected by completion of the EQ-5D-5L questionnaire. This will provide additional insight into the benefits of treatment with F901318.

Further detail has been added for efficacy and safety assessments to clarify the processes for these assessments and to improve the consistency of reporting.

**Description of Changes in Amendment 04:**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title page | Sponsor address in the UK has been deleted.<br>The Project Manager details have been updated. | The Sponsor address is now in Austria.<br>The [redacted] Project Manager has changed. |
| Synopsis;<br>Section 4.1 | The numbers of centres has been increased from 40 to 50. | The number of centres has been increased to facilitate enrolment of patients. |
| Synopsis;<br>Section 3.2;<br>Section 4.1;<br>Section 6.3.4;<br>Section 8.8.3 | Patient-reported outcomes have been added, to be collected by completion of the EQ-5D-5L questionnaire. | The EQ-5D-5L is a validated questionnaire to evaluate the effect of treatment on the patients quality of life, and will provide additional insight into the benefit profile of F901318. |
| Synopsis;<br>Section 3.4 | An Extended Treatment Exploratory Objective has been added: To describe the efficacy and safety of prolonged treatment with F901318 for infections due to resistant fungi in patients lacking suitable alternative treatment options. | It is estimated that approximately 25% of patients who respond to treatment with F901318 may require treatment beyond the maximum of 90 days of treatment included in the main phase of this protocol. Safety and efficacy data collected from the end of the main study phase onwards will be evaluated as an exploratory objective. |
| Synopsis;<br>Protocol body text throughout | Reference to treatment with F901318 beyond Day 90 '**via an extended dosing mechanism that is outside the scope of this protocol**' has been replaced by a description of '**an extended treatment phase**'. | This change provides a more structured approach to management of patients who have responded to treatment with F901318, and who have a clinical need and are likely to continue to benefit from extended treatment beyond Day 90 of the main study. |
| Synopsis;<br>Protocol body text throughout | The description of the Day 84, End of Study (EOS), End of Treatment (EOT), and follow-up (FU) visits have been amended to describe the reporting of these visits for patients who complete the study during the main study phase and for those who require extended treatment. In addition, separate EOS, EOT, and FU visits are described for the main study phase and for the extended treatment phase. | Additional detail has been provided to ensure key data from the main phase of the study are reported consistently and completely for all patients. Clarification of the data to be reported at the Day 84/EOS/EOT visit for patients who will receive extended treatment will ensure appropriate data are reported to evaluate the secondary endpoints of the main study. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis; Section 4.1; Section 6.1.1; Section 6.3; Section 6.4.2; Section 6.5; Table 3 | The frequency of visits and the assessments to be conducted during the extended treatment phase of the study have been added. | Assessment of the patients [redacted] during the extended treatment phase will ensure management of these patients is monitored, will facilitate timely reporting of safety issues, and will confirm if continued treatment is justified. |
| Synopsis; Section 4.3.1 | Text has been added to **Inclusion Criterion 6** to clarify the process of susceptibility testing. | The additional text describes the process for situations in which an isolate is not available for central laboratory testing. |
| Synopsis; Section 4.1; Section 6.3.2; Section 8; Section 8.2.4; Section 8.8; Section 8.9; Section 8.9.3; Section 8.11 | Text has been added to describe the inclusion of all efficacy, safety, and pharmacokinetics (PK) data from the main study phase (treatment up to Day 84/90/EOT and the subsequent 4-week FU) in the primary clinical study report, and the inclusion of efficacy, safety, and PK data from the extended treatment phase in the report addendum. | A two-stage approach to reporting the study data will allow timely reporting of the data supporting the objectives of the main study while allowing continued treatment of those patients who remain in the extended treatment phase of the study. |
| Section 2.4: Section 4.1 | **For patients going on to receive ET, the decision to continue to ET is based on the Investigator's assessment that the patient has benefited from therapy to date and that extended therapy will offer value and has a favourable benefit-risk for the patient** has been added to the benefit: risk statement. | Extended treatment is provided at the request of the Investigator, based on the Investigator's assessment of potential continued benefit. Extended treatment is to be discussed with the Medical Monitor (MM) and must be approved by the MM. |
| Section 4.1 | Figure 1 (Study Flow Diagram) has been extended to describe the extended treatment phase of the study, and is presented as 2 separate figures for different treatment scenarios. | Figure 1 and Figure 2 present a description of the progress of patients through the main study phase, and through the extended treatment phase for patients who are to receive continued treatment. |
| Table 1 | Rows have been added to the table for EQ-5D-5L and for Fungal Susceptibility testing, with explanatory footnotes. | The addition of these rows provides consistency with updates to the protocol synopsis and body text. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 4.1.1; Table 3 | Section 4.1.1 and Table 3 have been added to provide details of the assessments required during the extended treatment phase. | Guidance is provided to ensure patients who receive extended treatment are managed consistently, and data are recorded as required. |
| Section 4.2 | '**Extended treatment is justified for those patients who have benefited from treatment with F901318 but whose IFD has not completely resolved after 84 to 90 days of treatment and who would continue to benefit from further treatment with F901318. No alternative treatment options are available for these patients, and stopping treatment with F901318 after 84 to 90 days could entail a risk of IFD exacerbation**' has been added. | This text provides a rationale for extended treatment with F901318 in patients who have benefitted from treatment with F901318 and will continue to receive a benefit from continued treatment. |
| Section 4.3.1.1 | Inclusion criteria for the extended treatment phase have been added. | The Inclusion Criteria will ensure only eligible patients receive extended treatment with F901318. |
| Section 4.3.2.1 | Exclusion criteria for the extended treatment phase have been added. | The Exclusion Criteria will ensure only eligible patients receive extended treatment with F901318. |
| Section 4.3.4 | '**ALT or AST meet criteria for major enzyme elevation AND total bilirubin > 1.5x ULN (if baseline < ULN) OR > 1.5x baseline (if baseline > ULN) without evidence of obstruction, malignancy, impaired glucuronidation capacity or another explanation as detailed in Appendix 3. Study drug must be stopped, and patient follow-up must be conducted in accordance with Appendix 3**' has been added to the description of circumstances leading to patient withdrawal. | This text provides further detail of the changes in liver enzymes and bilirubin which require a patient to stop treatment with F901318, and provides consistency with other sections of the protocol relating to this issue. |
| Section 5.1 | Guidance on dose interruptions has been added. | The guidance will improve the consistency of management of patients when treatment with F901318 is interrupted. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 5.9; Section 6.2.6 | Further detail has been added to clarify the requirements for recording of prior and concomitant treatments. | The additional detail will improve the consistency of recording of prior and concomitant treatments. |
| Section 6.2.4 | Further detail has been added to clarify the requirements for recording of infectious disease history and microbiological assessments. | The additional detail will improve the consistency of recording of infectious disease history and microbiological assessments. |
| Section 6.3.1.4 | Detail has been added to describe the requirements for shipping of isolates, tissues, or biological fluid samples to an appropriate central laboratory for confirmation of diagnosis. | Correct collection and shipping of samples for central laboratory confirmation of diagnosis and susceptibility testing is an essential requirement of the study. |
| | Text has been added to describe the CSF findings for diagnosis of patients with coccidioidomycosis. | This text provides additional information concerning identification of patients with endemic fungal infection. |
| Section 6.4.1; Section 6.4.1.2 | Text has been added to further define adverse events and to describe in more detail the requirements for reporting adverse events. | The additional detail will improve the consistency of recording adverse events, and reinforces the requirements and responsibilities for reporting adverse events. |
| Section 6.4.2.2 | Text has been added to further define neutropenic status. | The detail clarifies the definition of neutropenia. |
| Appendix 2 | Changes have been made to definitions of invasive fungal diseases in anticipation of a planned update to the definitions. | The changes are being made before formal update of the definitions to improve the consistency of diagnosis over the course of the study. |

Further minor changes have been made throughout the protocol to correct typographical errors and to clarify text.

**Amendment 03 28 November 2018**

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**Overall Rationale for Amendment 03:**

The descriptions of End of Treatment and End of Study have been updated to clarify the process for patients who will receive ET with F901318 beyond the 90 days via an ET mechanism outside the scope of this protocol.

Description of the loading and maintenance doses of F901318 have been updated to acknowledge the fact that an exact mg/kg dose can not be achieved for most patients when whole 30 mg tablets are administered. A description of the formulation of F901318 tablets has been added.

The inclusion criteria have been updated to describe the process for enrolment of patients with multiple fungal infections, and to permit management of patients with resistant isolates in accordance with the Investigator's clinical judgement.

The exclusion criteria have been updated to clarify criteria or to remove restrictions based on current knowledge, and to implement exclusions which may be required by local regulatory authorities.

Information concerning concomitant medications and concomitant antifungal therapy has been updated to provide more detailed guidance.

A description of the possible circumstances and processes for study termination has been added.

The definitions of treatment success and failure have been updated to improve the consistency and clarity of these definitions. Further guidance has been added relating to prior and baseline symptoms, and to microbiological assessments.

The adverse events of special interest have been updated [redacted]

Additional information has been added to provide an improved description of the rationale for the sample size and the comparisons to be conducted on the study data.

Description of Changes in Amendment 03:

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title page | Product International Non-proprietary Name (INN) has been added. | The INN for F901318 had not yet been approved when the original protocol was written. |
| Title page | Sponsor address in Austria has been added. | The Sponsor has established a legal presence in Austria. |
| Synopsis; Section 5.1 | **In addition, treatment with F901318 may be continued to Day 90 in patients who are judged to need therapy beyond 90 days and who will receive treatment with F901318 via an extended dosing mechanism that is outside the scope of this protocol. For patients who are to receive extended treatment with F901318, the End of Treatment (EOT) and End of Study (EOS) for this protocol are taken as the day on which therapy stops under this protocol**, or similar text, has been added. | Patients who may benefit from extended treatment with F901318 for longer than 90 days will receive further treatment with F901318 outside of the scope of this protocol. |
| Synopsis; Section 4.1 Summary of Study Design | **For patients who will continue therapy beyond Day 90 under an extended dosing mechanism, the Day 84 visit and the EOT visit will be combined into a single Day 84/EOT visit on approximately Day 90 and there will be no 4-week FU visit,** or similar text, has been added. | For patients who will receive extended treatment, the EOT and the EOS occur at the same time, and no post-treatment follow-up is required after EOS/EOT |
| Synopsis; Section 4.1 Summary of Study Design; Section 4.2 Discussion of Study Design; Section 5.1 Treatments Administered; | The term '**approximately**' has been added to the description of the loading dose and maintenance dose regimen. | This change acknowledges the fact that an exact mg/kg dose can not be achieved for most patients when whole 30 mg tablets are administered. |
| Synopsis; Section 4.1 Summary of Study Design; Section 6.6 Pharmacogenomics | [redacted] r similar text, has been added. | [redacted] |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis;<br>Section 4.3.1<br>Inclusion Criteria | In General Inclusion Criterion 6, 'If the isolate is subsequently found to be resistant, study therapy may be **continued or** discontinued **based on clinical response at the discretion of the Investigator. Patients with infections due to multiple fungi can be enrolled provided at least one fungus is known or predicted to be F901318-susceptible AND the patient has limited alternative treatment options for that fungus as defined in Inclusion Criterion 7. As a specific example, a patient with simultaneous IA due to an azole-resistant strain and also invasive mucormycosis could be enrolled and treated with the combination of F901318 and isavuconazole. The choice of additional agents to treat other fungi should also consider the limitations applied to allowed medications. Cases of polyfungal infection should be discussed with the MM'** has been added**.** | Investigator discretion to continue treatment of patients with resistant isolates has been added to allow continued treatment of patients if the Investigator is confident a clinical benefit is achieved.<br><br>Enrolment of patients with infections due to multiple fungal species if at least one species is susceptible to F901318 will allow treatment of patients who have a mixture of susceptible and resistant fungal infections. |
| Synopsis;<br>Section 4.3.2<br>Exclusion Criteria | Exclusion Criterion 4 has been amended: Suspected zygomycosis **(mucormycosis) as the IFD used to qualify for the study** has been added. **Increased vigilance for the possibility of zygomycosis is required for suspected IA with negative baseline GM** has been added. '~~**and treatment should not be started or adapted. In particular, suspected IA with negative baseline galactomannan (GM) should generally trigger increased vigilance**~~' has been deleted. | This statement emphasizes to Investigators the lack of activity of F901318 against this fungal species. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis; Section 4.3.2 Exclusion Criteria | In Exclusion Criterion 7, endocarditis has been deleted as an example of a condition that 'may jeopardize adherence to the protocol requirements or impede the accurate measurement of efficacy.' | With the implementation of extended dosing approaches for selected patients, this example was judged overly restrictive. |
| Synopsis; Section 4.3.2 Exclusion Criteria | Exclusion Criterion 12d has been deleted: ~~**Intended use of new concomitant medications that prolong the QT/QTc interval**~~. | Nonclinical studies of F901318 have demonstrated minimal potential to affect the QT/QTc interval, and this has been confirmed in clinical studies showing a lack of effect on QT/QTc interval across the therapeutic exposure range. |
| Synopsis; Section 4.3.2 Exclusion Criteria | Detail has been added to Exclusion Criterion 14: **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 enrolment**. | The additional text identifies the prohibited concomitant medications, and provides context for consideration of other concomitant medications. Even though nonclinical biochemical testing predicts a lack of cross-over effects between human and fungual DHODH, concomitant therapy with inhibitors of the human DHODH enzyme has been prohibited as a precautionary measure. |
| Synopsis; Section 4.3.2 Exclusion Criteria | Exclusion Criterion 15 has been added: **Additional exclusion criteria required by local regulatory authorities**. | This exclusion criterion has been added to facilitate compliance with specific local regulatory authority requirements. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis: | Detail has been added to the Concomitant medication section: **Concomitant administration of teriflunomide and leflunomide is prohibited. There are no other absolutely prohibited or contraindicated medications. However, there are potential DDIs with F901318 and the choice of concomitant medications should take this into consideration** and **Data to date suggest that F901318 does not prolong the QTc interval, and concomitant agents with known potential to prolong the QTc interval may be used with caution. Ongoing therapy with an agent known to have a risk of QT prolongation is not a contraindication for enrolment provided the patient meets the requirements of Exclusion Criterion 12. After enrolment, initiation of new concomitant treatment with known QTc-prolonging agents must be discussed with and approved by the MM.** | The revised text provides more detailed guidance on the use of concomitant medication, and the rationale for this guidance. The guidance relates to specific medication with potential for drug-drug interaction, and medications which may affect the QT/QTc interval. |

| | | |
|---|---|---|
| Synopsis | The Concomitant Antifungal Therapy section has been revised: New text has been added: **In order to meaningfully analyse the efficacy of F901318, it is important to avoid concomitant use of other systemic antifungal agents with known or potential activity against the primary fungal infection. The constraints on the choice of additional agents may be complex and thus use of any other systemic concomitant antifungal or combination treatment (such as addition of terbinafine for confirmed *Lomentospora prolificans* infections or an echinocandin to manage infection due to Candida) is permitted but is discouraged.**<br>**Antifungal combinations should be based on the Investigator's clinical judgement and must be discussed with the MM.**<br>**Depending on the treatment given, an extra visit for Unscheduled Trough PK sampling (for TDM analysis of F901318) may be required 3 to 5 days after starting or stopping such concomitant medication, to assess potential DDIs and to enable dose adjustment of F901318 as needed. There is also the potential for further Unscheduled Trough PK samples to assess the impact of any dose adjustments made. In addition, an Unscheduled Intensive PK sampling day may be advised to evaluate the PK of F901318 and** [redacted]<br>Original text has been deleted: ~~**Use of concomitant treatment for Candida (or other yeast) infection with fluconazole or an echinocandin is permitted in all patients at any time during the study. An extra visit for Unscheduled Trough PK**~~ | The revised text provides more detailed guidance on the use of concomitant antifungal medication, and the rationale for this guidance. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | ~~**sampling (for TDM analysis of F901318) will occur 3 to 5 days after starting or stopping such concomitant medication, to assess potential DDIs and to enable dose adjustment of F901318 as needed, with the potential for further Unscheduled Trough PK samples to assess the impact of any dose adjustments made. In addition, an Unscheduled Intensive PK sampling day is advised to evaluate the PK of F901318 and** [redacted]~~<br>~~**Use of any other systemic concomitant antifungal or combination treatment (such as addition of terbinafine) for confirmed Lomentospora prolificans infections is permitted but is discouraged.**~~<br>~~**Antifungal combinations should be based on the Investigator's clinical judgement and must be discussed with the MM**~~. | |
| Synopsis | A note has been added to the Efficacy Endpoints: ***Note: For patients who will continue therapy beyond Day 90 under an extended dosing mechanism, the Day 84 visit and the EOT visit will be combined into a single Day 84/EOT visit on approximately Day 90 and there will be no 4-week FU visit.*** | This note describes the consolidation of the EOT and EOS visits for patients who will receive extended treatment with F901318, and that no post-treatment follow-up is required after EOS/EOT. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 2.1.2 F901318 has potential to address that unmet need | In paragraph 5, line 3, the phrase '~~**and has limited potential for DDIs**~~' has been deleted and replaced by '**with in vitro studies showing that it lacks phototoxicity potential. The CYP based metabolic profile of F901318 and its weak CYP inhibition potential means that DDIs can be predicted and managed, using Therapeutic Drug Monitoring (TDM) where appropriate**'. | The amended text provides more detail concerning the predictability and management of potential DDIs. |
| Section 2.1.3 Clinical Pharmacology | Text has been added to paragraph 7: [redacted] | Further information concerning the major metabolite of F901318 is presented. |
| | Text has been added after sentence 1 of paragraph 10: **Concomitant administration of inhibitors of human DHODH (teriflunomide and leflunomide) is prohibited.** | Prohibited medications are described. |
| Section 2.4 Risk Assessment | In paragraph 1, final sentence, the phrase '~~**elevated liver enzymes**~~' is deleted and replaced by [redacted]'. | The revised description provides more detail [redacted] han in the original text. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 4.1 Summary of Study Design | **Figure 1** has been added. | Figure 1 is a simple schematic to describe the overall design of the study. |
| | Paragraph 4, text has been added: **Patients with infections due to multiple fungi can be enrolled provided at least one fungus is known or predicted to be F901318-susceptible**. | The text has been added to describe the circumstances under which a patient with multiple fungal infection may be enrolled in the study. |
| | Paragraph 5, text has been deleted: ~~**On Day 1 of treatment, all patients weighing 75 kg or more will receive 300 mg of F901318 divided into 2 or 3 doses**~~. | This text is not required, and has been deleted to avoid possible confusion. |
| | **Table 1, Visit 12a at Day 35** has been added. | This visit is solely to take a blood sample to measure liver enzymes and bilirubin, to ensure continued monitoring and risk management. |
| | Table 1, various footnotes have been amended. | Footnotes have been amended to be consistent with changes to the protocol text. |
| Section 4.3.5 Study Termination | **Section 4.3.5** has been added. | The previous version of the protocol had no description of the possible circumstances and processes for study termination. |
| Section 5.1 Treatments Administered | Various minor text changes have been made. | Changes have clarified the text and provided further detail related to study drug treatment. |
| | **Table 3** has been added. | Table 3 describes the number and frequency of tablets to be administered relative to patient body weight. |
| Section 5.2 Identity of Investigational Products | Text has been added to describe the formulation of F901318 tablets. | The previous version of the protocol had no description of the formulation of F901318 tablets. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 5.9.1 Excluded Medications | Text has been added to describe prohibited medications.<br><br>**Section 5.9.1.1 Agents with a potential effect on the QT interval** has been added.<br><br>**Section 5.9.1.2 Interaction of F901318 with Concomitant Medication**, a brief summary of key points has been added.<br><br>**Section 5.9.2.1 Candida Prophylaxis and Concomitant Antifungal Therapy**; text has been added to paragraph 2 to provide perspective on the effect of other antifungal therapy on the analysis of efficacy. | Additional detail concerning the potential issues associated with the use of concomitant medications has been added to facilitate decisions taken by the Investigator. |
| Section 6.2.4 Infectious Disease History and Microbiological Assessments | The text of **Section 6.2.4 Infectious Disease History and Microbiological Assessments** has been amended to clarify the schedule for mycology, virology and bacteriology assessments. | Additional information has been provided to improve the consistency of recording data. |
| Section 6.3.1 Investigator's Assessment of Overall Response | Text has been added to **Section 6.3.1 Investigator's Assessment of Overall Response** to describe the assessment of response for patients who have multiple fungal infections. | Additional information has been provided to clarify the issues relating to patients with multiple fungal infections. |
| | Text has been added to **Section 6.3.1.1 Clinical Response** to clarify the recording of prior symptoms and baseline symptoms, particularly for patients who are asymptomatic at baseline. | Additional information has been provided to clarify the procedures for recording prior symptoms and baseline symptoms. These changes habe been approved by the Data Review Committee. |
| | In **Section 6.3.1.1 Clinical Response,** the definitions of Resolution-Complete and Resolution-Partial have been extended to provide further detail. | Additional information has been provided to clarify the definitions of resolution. |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 6.4.1 Adverse Events | In **Section 6.4.1 Adverse Events**, text has been added to describe the recording and reporting requirements for adverse events of special interest. | Further detail has been added to describe the procedures for recording adverse events of special interest. |
| | A new adverse event of special interest was added: **Changes in ALT or AST if > 3xULN and total bilirubin > 2xULN**. | This ensures that any cases meeting the rule for Hy's Law are reported and assessed by the Sponsor's hepatic advisory review process, even if baseline liver biochemistry values were already close to meeting the Hy's Law rule. |
| | A description of [redacted] has been added to **Table 6**. | The table has been amended to ensure [redacted] are reported as adverse events of special interest. |
| Section 8.1 Determination of Sample Size | Text has been added to **Section 8.1 Determination of Sample Size** to provide more information on the rationale for the sample size assumptions. | The additional information provides an improved description of the rationale for the sample size and the comparisons to be conducted on the study data. |

**Amendment 02 02 May 2018**

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

**Overall Rationale for Amendment 02**

The loading dose and maintenance dose have been changed from fixed doses to weight-related doses, the frequency of dosing with F901318, and the rationale for dose adjustment have been changed based on emerging data from Phase I studies.

The exclusion criteria have been modified to allow inclusion of patients with newly diagnosed HIV infection and patients receiving stable doses of concurrent medication with the potential to prolong the QT interval.

The handling of susceptibility testing information received after enrolment has been clarified.

The text referring to methods of birth control has been amended to be consistent with the Clinical Trial Facilitation Group definition of highly effective methods of contraception. (These changes are also included in Local Amendment 01-01.)

The background information has been updated to describe emerging data from Phase I studies in healthy volunteer subjects.

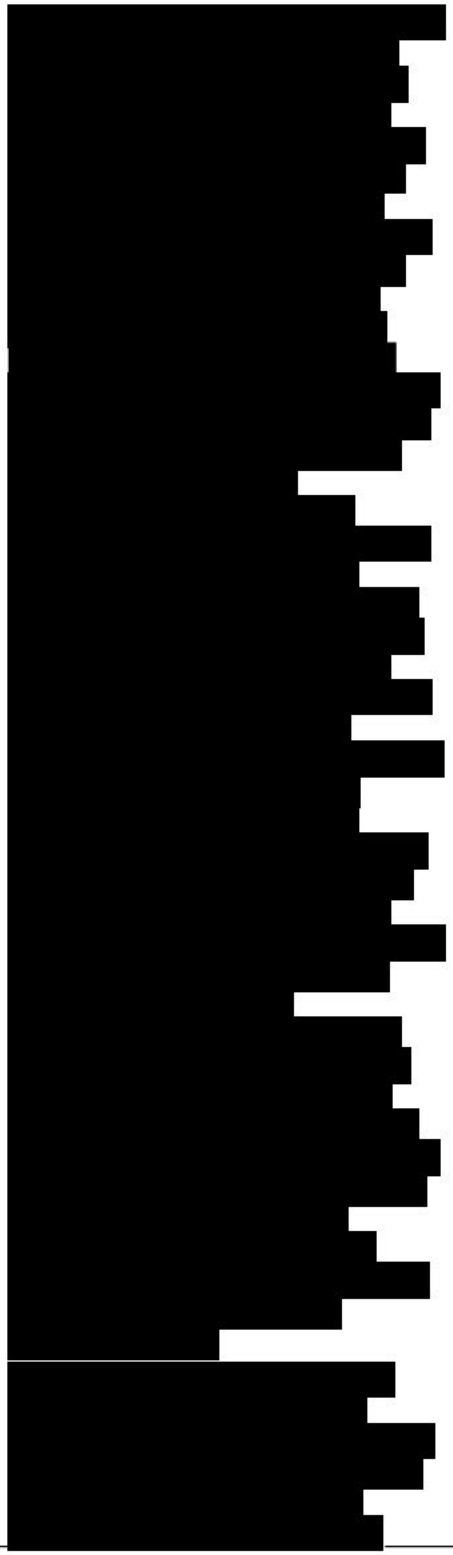
The definitions of treatment success and failure have been updated to improve the consistency and clarity of these definitions.

**Summary of Changes in Amendment 02**

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| **Synopsis;**<br>**Section 4.1 Summary of Study Design;**<br>**Section 4.2 Discussion of Study Design;**<br>**Section 5.1 Treatments Administered** | The loading dose has been changed from **120 mg every 12 hours** to **4 mg/kg divided into 2 or 3 doses**.<br>The maintenance dose has been changed from **60 mg twice daily** to **2.5 mg/kg/day divided into 2 or 3 doses**.<br>**A maximum daily dose of 300 mg, divided into 2 or 3 doses, has been included.** | The amended text is based on emerging data from Phase I studies in healthy volunteer subjects.<br>The maximum daily dose has not previously been defined. |
| **Synopsis;**<br>**Section 4.3.1 Inclusion Criteria** | For Inclusion Criterion 6, **Enrolment is based on presumed F901318 susceptibility for categories a-c and selected other species as described in the IB. For IFD due to isolates from species of uncertain susceptibility, enrolment may occur with the approval of the MM before isolate susceptibility is confirmed. If the isolate is subsequently found to be resistant, study therapy may be discontinued** has been added. | This amendment will allow prompt enrolment of patients while susceptibility testing is underway. |
| **Synopsis;**<br>**Section 4.3.2 Exclusion Criteria** | For Exclusion Criterion 6, **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** has been added. | This amendment will allow patients with newly diagnosed HIV infection to be included in the study. |
| **Synopsis;**<br>**Section 4.3.2 Exclusion Criteria** | The text of Exclusion Criterion 12d, has been changed from **Use of concomitant medications proven to prolong the QT/QTc interval** to **Intended use of new concomitant medications proven to prolong the QT/QTc interval**. | This amendment will allow patients who, at the time off enrolment, are receiving a stable dose of concomitant medication with the potential to prolong the QT/QTc interval and have a QTcF interval < 500 msec to be included in the study. |
| **Synopsis;**<br>**Section 5.1 Treatments Administered** | **An adjustment to loading and/or maintenance doses of F901318 may be required for patients who are being treated with drugs that either inhibit or induce CYP enzymes (or if such drugs are started or stopped)** has been added.<br>**An adjustment to the maintenance dose of F901318 may be required if patients develop abnormal liver enzymes, or if trough plasma levels of F901318 are outside the target range** has been added. | The amended text clarifies factors which can initiate dose adjustment. |

| | | |
|---|---|---|
| **Synopsis;**<br>**Section 5.1 Treatments Administered;**<br>**Section 5.6 Selection and Timing of Dose for Each Patient** | **A dose adjustment may be required for patients weighing between 40 kg and 60 kg** has been deleted. | This text is no longer required, as the amended dosage regimen is based on body weight. |
| **Synopsis**<br>**Section 4.3.1 Inclusion Criteria** | The text of Inclusion Criterion 4c has been changed from<br>**(hormonal implants, oral or injected hormonal contraceptives, intrauterine devices, two barrier methods such as a condom and a cervical cap) throughout the course of the study period. Reliable sexual abstinence is acceptable as a highly effective method of birth control for the purposes of this study. Periodic abstinence (e.g. calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception**<br>to<br>**throughout the course of the study period:**<br>**i) Established use of oral, injected, transdermal, intravaginal or implanted hormonal methods of contraception associated with inhibition of ovulation**<br>**ii) Placement of an intrauterine device or intrauterine hormone-releasing system**<br>**iii) Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)**<br>**iv) Bilateral tubal occlusion**<br>**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)**.<br>In the text of Inclusion Criterion 5, **abstain** has been changed to **totally abstain**, and **reliable** has been changed to **highly effective**. | The amended text is consistent with the Clinical Trial Facilitation Group definition of highly effective methods of contraception.<br>These changes are also included in Local Amendment 01-01. |

| | | |
|---|---|---|
| **Section 4.3.3 Patient Restrictions** | In the bullet referring to Female patients of child bearing potential:<br>**Established use of oral, injected or implanted hormonal methods of contraception**<br>has been changed to<br>**Established use of oral, injected, transdermal, intravaginal or implanted hormonal methods of contraception associated with inhibition of ovulation.**<br>**Placement of an intrauterine device or intrauterine system**<br>has been changed to<br>**Placement of an intrauterine device or intrauterine hormone-releasing system**.<br>**Double barrier method of contraception, such as condom and occlusive cap (diaphragm or cervical/ vault caps) with spermicidal foam/gel/ film/cream/suppository** has been deleted.<br>**Bilateral tubal occlusion** has been added.<br>**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** has been added.<br>In the bullet referring to Male patients with female partners of childbearing potential:<br>**reliable** has been changed to **highly effective.** | |

| | | |
|---|---|---|
| **Section 2.1.3 Clinical Pharmacology** | **More than 200** has been updated to **294**. **A total of 249 subjects have received F901318 in completed studies, with a further 45 subjects receiving F901381 in an ongoing multiple oral dose study** has been added.  | The amended text is based on emerging data from Phase I studies in healthy volunteer subjects. |

| | | |
|---|---|---|
| | [redacted] | |
| **Section 4.2 Discussion of Study Design** | [redacted] | The amended text is based on emerging data from Phase I studies in healthy volunteer subjects. |
| **Section 5.5 Selection of Doses in the Study** | **Limiting the total daily dose of F901318 to a dose of ≤ 3 mg/kg ($C_{max}$ is maintained below 4 µg/mL)** [redacted] | The amended text is based on emerging data from Phase I studies in healthy volunteer subjects. |
| **Section 5.7 Therapeutic Drug Monitoring** | The guidance for dose adjustment has been amended to include [redacted] **n Appendix 3 of the protocol.** | The amended text clarifies factors which can initiate dose adjustment. |

| | | |
|---|---|---|
| **Section 6.3.1.1 Clinical Response** | **Resolution of all attributable clinical symptoms and physical findings (i.e. resolution of all clinical symptoms and physical findings of IFD present at baseline and resolution of any clinical symptoms and physical findings of IFD that appeared at a subsequent visit and no new clinical symptoms and physical findings of IFD at that visit)** has been changed to **Resolution-Complete: Resolution of all attributable clinical symptoms and physical findings of IFD present at baseline or that appeared at a subsequent prior visit AND no new clinical symptoms and physical findings of IFD at the current visit.**<br><br>**Resolution of some attributable clinical symptoms and physical findings (i.e. resolution of some but not all clinical symptoms and physical findings of IFD present at baseline and/or of some but not all clinical symptoms and physical findings of IFD that appeared at a subsequent visit and no new clinical symptoms and physical findings of IFD at that visit)** has been changed to **Resolution-Partial: Some persistence of the attributable clinical symptoms and physical findings of IFD noted either at baseline or at a subsequent prior visit but there is improvement in at least some of these same symptoms and findings AND no worsening of any of these same symptoms and findings AND no new clinical symptoms and physical findings of IFD at the current visit.**<br><br>**No resolution of any attributable clinical symptoms and physical findings and/or worsening (i.e. no resolution or worsening of any clinical symptoms and/or physical findings of IFD present at baseline and of clinical symptoms and physical findings of IFD that appeared at a subsequent visit and/or appearance of new clinical symptoms and physical findings of IFD at that visit)** has been changed to **Failure-Stable: Neither worsening nor improvement in any attributable clinical symptoms and physical findings present at baseline or that** | The amended text clarifies the definitions of treatment success and treatment failure and improves consistency between the definitions. |

| | | |
|---|---|---|
| | **appeared at a subsequent prior visit AND no new clinical symptoms and physical findings of IFD at the current visit.**<br><br>**Failure-Progression: Shows EITHER worsening in one or more attributable clinical symptoms and physical findings present either at baseline or that appeared at a subsequent prior visit OR appearance of new clinical symptoms and physical findings of IFD at the current visit** has been added. | |
| **Section 6.3.1.2 Radiological Response** | **in aggregate (across all lesions if more than one lesion)** has been added to the definitions referring to improvement.<br><br>**< 25 % improvement** has been changed to **No change (0%) to < 25 % improvement**.<br><br>**Worsening in aggregate (across all lesions if more than one lesion)** has been added. | The amended text clarifies the definitions of treatment success and treatment failure and improves consistency between the definitions. |

| | | |
|---|---|---|
| **Section 6.3.1.5 Investigator's Assessment of Overall Response** | **Table 4 has been updated:**<br><br>**Success-Complete** has been changed from:<br>**• Resolution of all clinical symptoms and physical findings associated with IFD;**<br>**• Resolution of radiological abnormalities (≥90% response in some cases);**<br>**• Presumed or documented eradication.**<br>to:<br>**• Clinical: Shows resolution of all attributable clinical symptoms and physical findings associated with IFD (Resolution Complete);**<br>**AND**<br>**• Radiological: Shows resolution of radiological abnormalities (≥90% response);**<br>**AND**<br>**• Mycological: Meets criteria for presumed or documented eradication**.<br><br>**Success-Partial** has been changed from:<br>**• Resolution of some clinical symptoms and physical findings associated with IFD;**<br>**• Improvement of radiological abnormalities (at least 25% response at Day 42 or 50% at Day 84);**<br>**• Presumed or documented eradication.**<br>to:<br>**• Clinical: Shows resolution or improvement of some or all attributable clinical symptoms and physical findings of IFD, with no worsening of any previously noted clinical symptoms or physical findings and no new clinical symptoms or physical findings of IFD (Resolution-Complete or Resolution-Partial);**<br>**AND**<br>**• Radiological: Shows resolution or improvement of radiological abnormalities (at least 25% response);**<br>**AND**<br>**• Mycological: Meets criteria for presumed or documented eradication.** | The amended text clarifies the definitions of treatment success and treatment failure and improves consistency between the definitions. |

| | | |
|---|---|---|
| | **Failure-Stable** has been changed from:<br>**• Minor or no change in clinical symptoms and physical findings;**<br>**• Radiographic abnormalities associated with IFD but no evidence of progression OR < 25% improvement of radiological abnormalities.**<br>to:<br>**• Clinical: No improvement and no worsening of any attributable clinical symptoms and physical findings previously noted and no new attributable clinical symptoms or physical findings of IFD (Failure-Stable);**<br>**OR**<br>**• Radiological: Shows no evidence of progression OR < 25% improvement of radiological abnormalities;**<br>**OR**<br>**• Mycological: Had mycological evidence at baseline AND does not meet criteria for presumed or documented eradication.**<br><br>**Failure-Progression** has been changed from:<br>**• Evidence of progression based on clinical, radiologic and mycological criteria;**<br>**• Worsening or new clinical symptoms and physical findings and/or radiographic abnormalities associated with IFD;**<br>**• Alternative systemic antifungal treatment required.**<br>to:<br>**• Clinical: Either worsening of attributable clinical symptoms or physical findings of IFD or appearance of new attributable symptoms or findings of IFD (Failure-Progression);**<br>**OR**<br>**• Radiological: Worsening or new radiological abnormalities;**<br>**OR**<br>**• Mycological: Has mycological evidence for a recurrent or emergent IFD, OR alternative systemic antifungal treatment required.** | |

| | | |
|---|---|---|
| **Throughout** | Minor editorial and document formatting revisions | Minor, therefore have not been summarized |

## Amendment 01: 24 January 2018

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

## Overall Rationale for Amendment 01

Analysis of pharmacokinetic data from Phase 1 studies in healthy volunteers supports the use of a twice daily dosage regimen of F901318 to provide exposure within the predicted therapeutic range. The frequency of dosing has been changed from 4 times daily to 2 times daily based on these pharmacokinetic data. The frequency of blood sample collection when Intensive PK is being assessed has been amended to be consistent with the change in dose frequency.

## Summary of Changes in Amendment 01

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| **Synopsis**<br>**Section 4.1 Summary of Study Design**<br>**Section 5.1 Treatment Administered**<br>**Section 5.6 Selection and Timing of Dose for Each Patient** | The frequency of dosing with F901318 has been changed from **4 times daily** to **2 times daily**. | This change is based on emerging data from Phase I studies in healthy volunteer subjects. |
| **Synopsis**<br>**Section 4.1 Summary of Study Design** | Possible revision of the dose scheduled has been changed from **90 mg 3 times daily** to **total daily dosages of up to 240 mg divided into two or three doses**. | This change is based on emerging data from Phase I studies in healthy volunteer subjects. |
| **Synopsis**<br>**Section 4.1 Summary of Study Design** | The frequency of blood samples taken for pharmacokinetic analysis has been changed from [redacted] | The schedule of taking samples for pharmacokinetic analysis has been changed to match the change from a 4 times daily dosage regimen to a 2 times daily dosage regimen. |
| **Synopsis**<br>**Section 4.3.1 Inclusion Criteria** | Inclusion Criterion 7 g) has been modified to clarify the inclusion requirement. | The clarification reinforces the requirement for Medical Monitor approval for patients enrolled under this criterion. |
| **Section 5.12 Study Drug Accountability** | Study drug supply has been changed from **bottles sufficient for 1 week of dosing** to **bottles sufficient for 2 weeks of dosing**.<br>The amount of study drug supplied to the patient has been changed from **a maximum of 2 weeks of dosing** to **a maximum of 4 weeks of dosing.** | The study drug supply has been changed to match the reduction in the total daily maintenance dose from 240 mg daily to 120 mg daily. |
| **Synopsis**<br>**Section 6.4.3.4 Ophthalmologic Examination**<br>**Section 8.2.4 safety Endpoints** | The requirement for [redacted] | This change will facilitate patient management. [redacted] |
| **Table 1 Schedule of Events** | Table 1 has been amended to be consistent with changes to the text of the protocol. | To provide consistency within the protocol. |
| **Table 2 Schedule of Blood Sampling for Intensive PK Analysis** | Table 2 has been amended to be consistent with changes to the text of the protocol. | To provide consistency within the protocol. |
| **Throughout** | Minor changes have been made to ensure consistency with the change of dosage regimen | Minor, therefore have not been summarized |
| **Throughout** | Minor editorial and document formatting revisions | Minor, therefore have not been summarized |