Statistical Analysis Plan

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

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STATISTICAL ANALYSIS PLAN

F901318/0032

AN OPEN-LABEL SINGLE-ARM PHASE IIB STUDY OF F901318 AS TREATMENT OF INVASIVE FUNGAL INFECTION DUE TO *LOMENTOSPORA PROLIFICANS*, *SCEDOSPORIUM* SPP., *ASPERGILLUS* SPP., AND OTHER RESISTANT FUNGI IN PATIENTS LACKING SUITABLE ALTERNATIVE TREATMENT OPTIONS.

AUTHOR: [redacted]
VERSION NUMBER AND DATE: V3.0, 06APR23

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F2G Ltd.
PROTOCOL F901318/0032

Statistical Analysis Plan

Page 3 of 101

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Authors	Significant Changes from Previous Authorised Version
1.0	18Aug2021	[redacted]	Not Applicable – First Draft
2.0	28Feb2022	[redacted]	Section 7.4 Included details of deriving -azole resistance subcategory using local laboratory data, since central lab data was not available for all patients. Section 12.1 Included details for imputation of partial and missing dates for medications. Section 14 Added categories Duration of exposure details. Section 16.1.7.5 Added details for ascertaining survival status where survival status was not collected in the eCRF. Section 16.1.7.5 Added specification that Kaplan-Meier plots will be truncated when the number of patients at risk is <5. This is due to large degree of uncertainty leading to potentially misleading interpretation. Section 18.4.2 Systolic Blood Pressure markedly abnormal high criteria amended to >=140 mmHg based on advice from safety physicians.

3.0	17Mar2023	[redacted]	Section 7.4 added subgroup for Reason for Limited Treatment Options and updated neutropenia status derivation. Section 17 added subgroups (concomitant medication, demographaics and underying disease) Sectoin 17.1 further defined accepatbel sampling widnow for trough samples Section 17.1.1 revised analysis for assessing impact of concomitant medications upon olorofim exposure Section 18.2.1 added derivation for Creatinine clearance Section 18.3.2 added definition of retrospective and prospective ECG overreads.

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, pharmacokinetic (PK) and safety data for protocol F901318/0032. It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 01 dated 19 Dec 2017, amendment 01 dated 24 Jan 2018, amendment 01-01 dated 07 Mar 2018, amendment 02 dated 02 May 2018, amendment 03 dated 28 Nov 2018, amendment 4 dated 03 May 2019, amendment 5 dated 30 Oct 2019 and amendment 6 dated 28 Feb 2020. However protocol amendment 5 has no impact on the SAP.

A data review (DR) plan will be set up for this study and will pertain to the SAP.

2. STUDY OBJECTIVES AND ESTIMANDS

2.1. PRIMARY OBJECTIVE

The primary objective is:

To 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.

2.2. SECONDARY OBJECTIVES

The secondary objectives 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.
- To describe the efficacy of F901318 in terms of Investigator-assessed overall response (integrating clinical, radiological and mycological response).
- To describe all-cause mortality.
- To characterize PK of study drug and metabolite(s) including effects of dose adaptations.
- To evaluate patient-reported outcomes based on the European quality of life – 5 dimensions (EQ-5D-5L)

questionnaire.

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To evaluate dose adaptation and drug-drug interaction (DDI) management strategies.
- To assess potential drug interactions associated with F901318 treatment.

2.4. EXTENDED TREATMENT EXPLORATORY OBJECTIVES

[redacted]

2.5. ESTIMANDS

Not applicable.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

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 rate of enrolment 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 have invasive fungal disease (IFD) which can be classified into one of five categories:

- Lomentospora (Scedosporium) prolificans (LoPro),
- Scedosporium spp.,
- Aspergillus spp.,
- Other F901318-susceptible fungi (as described in the Investigator Brochure [IB] or based on information provided by the Medical Monitor [MM], and in either case requiring approval of the MM), or
- Probable Lower Respiratory Tract Disease (LRTD) Invasive Aspergillosis (IA) 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, but not meeting the criteria for culture proven invasive fungal infection.

Lifecycle Safety-CEVA Endpoint Adjudication Committee Charter documents these baseline categorization of IFD.

The first four categories require proven IFD. Diagnosis may be based on culture, polymerase chain reaction (PCR), or other acceptable methods. For patients with confirmed fungal infection no specific diagnosis method is required. The fifth category refers to probable LRTD IA, which must meet the EORTC/MSG criteria. All patients with IA must have galactomannan (GM) tests completed before enrolment. The initial diagnosis of IFD will be based on the Investigator assessment to minimise 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 and the patient has limited alternative treatment options for that fungus as defined in Inclusion Criterion 7.

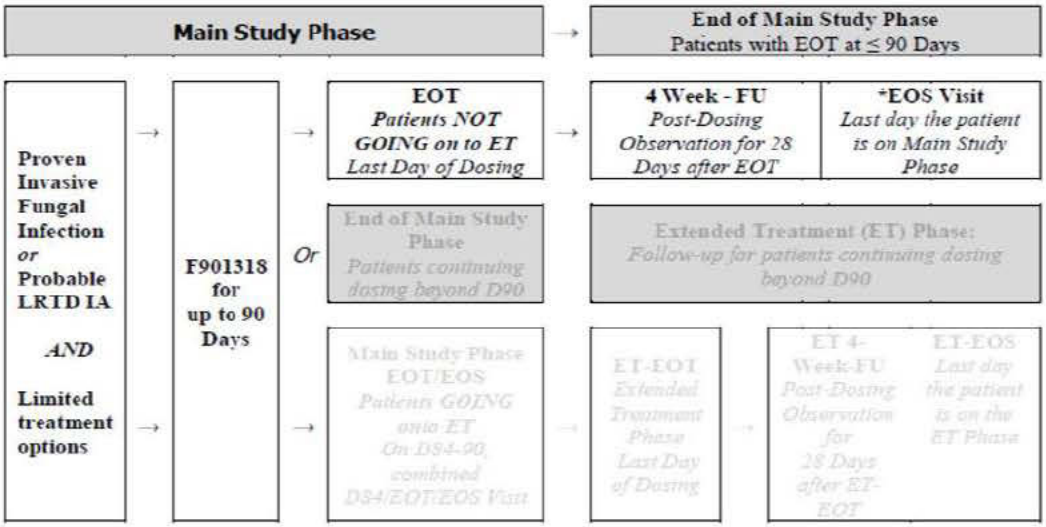
The study has two phases: the main study phase (Figure A) and the extended treatment phase (Figure B).

Up to and including protocol amendment 4 patients will receive a loading regimen of approximately 4 mg/kg of F901318 divided into two or three doses (12 or 8 hours apart respectively), followed by a maintenance regimen of approximately 2.5 mg/kg/day divided into two or three doses from Day 2 onwards. Based upon emerging data from studies in healthy volunteers, the recommended dose regimen may be revised to total daily dosages of up to 300 mg divided into two or three doses.

From protocol amendment 6 onwards patients will receive a one-day oral loading dose of 150 mg bid (dosed 12 ± 1 hours apart) followed by a maintenance dose regimen of 90 mg bid (dosed 12 ± 1 hours apart) from Day 2 onwards. 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.

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 seven 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 to 83 (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. 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 likely to continue to benefit from extended treatment. In the case of patients proceeding to the extended treatment phase, the end of treatment (EOT) and end of study (EOS) are taken as the day therapy is completed in the main study phase. Patients in the main study phase who complete the EOT visit, will have a 4-week follow-up assessment 28 days after EOT. Patients in the extended treatment phase will not have the 4-week follow-up assessment 28 days after main study EOT, but will complete extended treatment phase follow-up visits on a four weekly basis, and a last visit four weeks after the end of extended treatment.

Figure A: Study flow diagram; main study phase



Abbreviations: 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 follow-up visit is not

necessarily the EOS for all patients as Day 42 and Day 84 are required for all patients (if successful outcome then required assessments will be performed; if unsuccessful outcome, then survival status will be obtained), if treatment is stopped prior to Day 42 or Day 84 the Day 42 and/or Day 84 may occur after the 4-week follow-up visit.

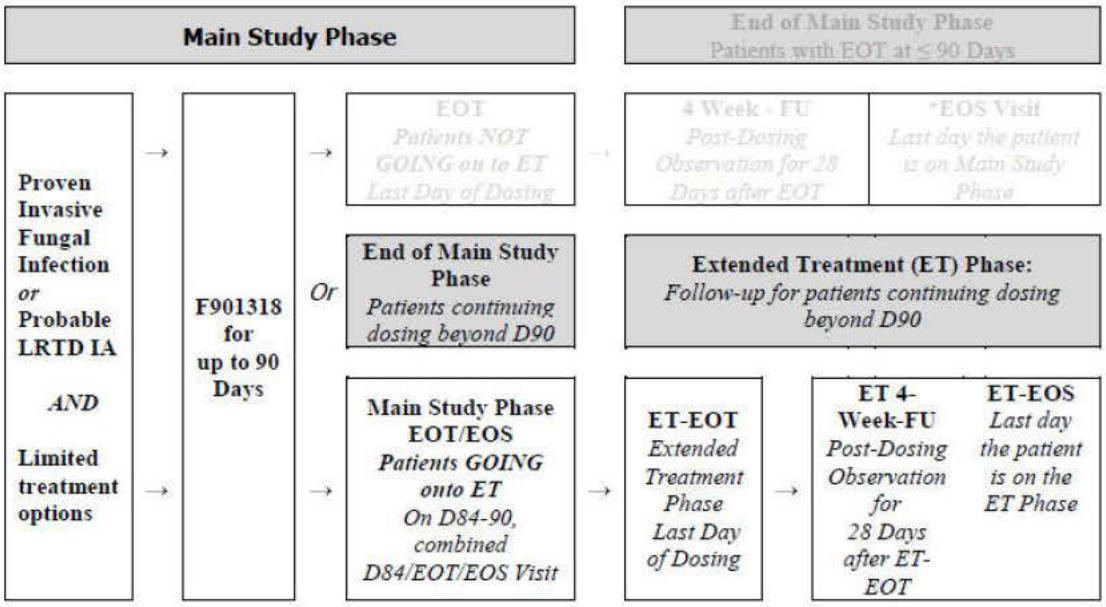
The Initial Clinical Study Report (CSR) will be prepared when 100 patients have completed the EOS visit in the main study phase (the first data cut-off date). The Initial CSR will include all main study phase data and available extended phase data for the 100 patients up to the first data cut-off date.

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.

[redacted]

Data for those patients who have completed the EOS visit in the main study phase and have entered the extended treatment phase of the study will be displayed in narratives for the Initial CSR, Final CSR [redacted] analyses. Narratives will be produced by [redacted] Medical Writing and will include main study and extended treatment phase data.

Figure B: 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.

[redacted]

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in section 4.1 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

- Protocol amendment 6 section 8.9.4.3 states that changes in [redacted]

[redacted]

- An additional listing was added to the analysis of Disposition (section 9.1) to present all patients whose trial participation was impacted by COVID-19 and to describe the particular impact.
- All protocol deviations relating to COVID-19 will in addition be summarised, and a by patient listing with the specific details will be provided.
- Protocol amendment 6 section 8.7 states that Medications will be presented by Anatomical Therapeutic Chemical (ATC) class and Preferred Term. As the same Preferred Term occurs in more than one ATC term, it was decided to only present by ATC level 4, and not by Preferred Term as well.
- The per-protocol analysis set (PPAS) is added to SAP which was not mentioned in protocol amendment 6.
- Definition of Intensive PK set is modified in SAP from protocol amendment 6.
- "Summary tables of AST/ALT elevations in association with nausea, vomiting, anorexia, abdominal pain, fatigue" removed from SAP since it was not feasible to identify elevations in association with symptoms, and elevations and AESI are already thoroughly identified and summarized.
- "Patient-reported outcome [redacted] endpoint is not mentioned in protocol however it is added in SAP.
- Change in terminology "interim analysis" to "analysis for initial CSR".
- Change in terminology [redacted]
- Summaries of serum GM by visit will be presented to assess changes in serum GM from baseline.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for Independent Data and Safety Monitoring Board (IDSMB) meetings
- Analyses for DRC meetings
- Analyses for the initial CSR
- Final Analysis
- [redacted]

4.1. INDEPENDENT DATA & SAFETY MONITORING BOARD (IDSMB)

IDSMB output templates, portraying proposed data displays, will be provided by IQVIA Biostatistics as a separate document.

4.2. DRC ANALYSES

DRC patient profile output templates, portraying proposed data displays, will be provided by IQVIA Biostatistics as a separate document.

4.3. ANALYSES FOR INITIAL CSR

F901318 has been granted Breakthrough Therapy Designation by the Food and Drug Administration (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 CSR analysis will take place for this study once 100 patients have completed the EOS visit in the main study phase. [redacted] The analyses used to support this Initial CSR analysis will include all main study phase data and available extended phase data for the 100 patients up to the point of the EOS visit in the main study.

Data for those patients who have completed the EOS visit in the main study phase and have entered the extended treatment phase of the study will be displayed in narratives for the Initial CSR. Limited safety data and efficacy endpoints for extended phase will be summarised. Narratives will be produced by [redacted] Medical Writing and will include main study and extended treatment phase data.

Derivations and definitions for the initial analysis will be based on those required for the final analysis contained in this SAP, unless deviations are stated within the text. All outputs planned for the final analysis will be provided for the initial analysis.

4.4. FINAL ANALYSIS

All analyses identified in this SAP will be performed by [redacted] Biostatistics following F2G Ltd. authorisation of this SAP, database lock, and F2G Ltd. authorisation of analysis sets.

5. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to the clinical database lock for the initial and final analyses of the study.

A Data Review (DR) plan will be created containing more details on the derivations of analysis sets and review of these by F2G Ltd.

5.1. PROCESS FOR ANALYSIS SET ASSIGNMENT

- Prior to clinical database lock for both initial and final analyses, data reviews will be performed to meet the following objectives:
  - Establish analysis set assignment.
  - Identify the potential reason(s) for exclusion of patients from one or more of the analysis sets. From a statistical perspective, the reason(s) for exclusion may be protocol deviations (identified during the clinical conduct of the study) or other factors affecting the efficacy outcome or treatment of the patient.
  - Identify underlying data issues affecting the integrity of the analyses on an ongoing basis during the clinical conduct of the study and to discuss any such issues impacting the efficacy analyses or requiring revision to the SAP prior to clinical database lock.
- A minimum of two weeks prior to each data review meeting the following will be delivered to IQVIA Biostatistics:
  - A clean snapshot of the database.

- The data handling report.
- The Clinical trials management system (CTMS) protocol deviation (PD) log (built up during the clinical conduct of the study and reviewed at scheduled protocol deviations review meetings; authorised prior to the final analysis clinical database lock).
- Any other information that may impact the decisions regarding the assignment of patients to the analysis sets.

- [redacted] Biostatistics will then produce the following documents to be delivered to F2G Ltd. at least two business days prior to each data review meeting:
  - DR plan.
  - Appendix 1: Assignment of Patients to Analysis Sets and Reason(s) for Exclusion (EXCEL Spreadsheet).
- As part of the process of analysis set assignment [redacted] Biostatistics will consider the following:
  - Analysis set definitions may be definitively determined algorithmically from the study database according to the rules.
  - Analysis set definitions may require supplemental data that does not form part of the clinical database to make assignment decisions; such information must be documented and authorised by F2G Ltd. prior to the final analysis clinical database lock.
  - In support of analysis set assignments a selection of by-patient data listings may be prepared and delivered to F2G Ltd. as part of data review package.
  - The data handling report, Biostatistics data issues log, CTMS PD log and other supplemental data may be considered in addition and may be delivered to F2G Ltd. as part of the data review package.
- During the data review meeting, [redacted] Biostatistics will document the following in meeting minutes which can take the form of an EXCEL spreadsheet (recommended), report or actual meeting minutes document:
  - Decisions regarding analysis set assignment and reason(s) for exclusion of patients.
  - Decisions regarding data issues as identified in the data handling report and Biostatistics data issues log potentially impacting the planned analyses.

- Patient-level decisions (for example, not to exclude a patient when an exclusion rule indicates the patient meets an exclusion criterion), with accompanying explanations.

- Following the data review meeting, [redacted] Biostatistics will follow up on actions as discussed at the data review meeting, for example additional data issues requiring query to sites.
- Once all outstanding actions items discussed during the data review meeting are resolved, [redacted] Biostatistics delivers the final data review report to F2G Ltd. for authorisation.
- After finalisation of the analysis set assignments (i.e. F2G Ltd. authorisation of the final data review report), [redacted] Biostatistics will add the analysis set flags and variable(s) indicating reason(s) for exclusion to the ADSL dataset.

5.2. ALL PATIENTS ENROLLED SET [ENR]

The all patients enrolled (ENR) set will contain all patients who provide written informed consent for this study.

5.3. INTENT-TO-TREAT SET [ITT]

The intent-to-treat (ITT) set will contain all patients in the ENR set who receive at least one dose of study medication.

5.4. MODIFIED INTENT-TO-TREAT [MITT]

The modified intent-to-treat (mITT) set will contain all patients in the ITT set who are assigned to a DRC-adjudicated disease category (see Section 3.1, and process documented in DRC charter). The mITT population and sub-populations based on DRC-adjudicated disease categories will be used for the analysis of efficacy data.

5.5. PER-PROTOCOL ANALYSIS SET [PPAS]

The per-protocol analysis set (PPAS) will contain all patients in the mITT who complete the main study phase and have no major/critical protocol deviations during the main study phase that will impact the efficacy assessment. Protocol deviations will be reviewed on a case-by-case basis by the medical advisor to help determine the exclusions from the per-protocol set. Answers to inclusion/exclusion criteria will not be checked programmatically by [redacted] Biostatistics in consideration for exclusion from the PPAS. The responsibility for checking inclusion/exclusion criteria lies with Data Management.

Complete details on protocol deviations considered to impact efficacy and reasons for exclusion will be documented in the DR plan.

5.6. SAFETY ANALYSIS SET [SAF]

The safety analysis set (SAF) will contain all patients who receive at least one dose of study medication (or part thereof).

If there is any doubt whether a patient was treated or not, they will be assumed treated for the purposes of analysis.

5.7. TROUGH PK ANALYSIS SET [TROUGH PK SET]

The trough PK analysis set (Trough PK set) will contain all patients who received at least one dose of study medication and have at least one valid measured trough F901318 plasma concentration. A valid trough sample should include date, time and trough value.

5.8. INTENSIVE PK ANALYSIS SET [INTENSIVE PK SET]

The intensive PK analysis set (Intensive PK set) will consist of the subset of patients in the SAF population who have an evaluable intensive PK profile from which at least one PK parameter can be determined.

6. GENERAL CONSIDERATIONS

Analyses will generally be descriptive in nature with efficacy data presented overall and by Baseline DRC-adjudicated disease category using appropriate summary statistics. Safety data will be presented overall only. Categorical data will be described using absolute and relative frequencies (n and %). Percentages will be presented to 1 decimal place. Continuous data other than PK will be presented using descriptive statistics (n, mean, standard deviation [SD], minimum, median and maximum). The precision of the measurement for each continuous variable will be used to determine the number of decimal places to present in tables, figures and listings, as specified in appendix 1. Minimum and maximum values will be reported with the same precision as the unit of measure. For detail on PK data presentation refer to Section 17.

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

6.1. REFERENCE START DATE AND STUDY DAY

Reference start date is defined as the date of the first dose of study medication, (Day 1 is the day of the first dose of study medication).

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Study Day will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:

  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date, then:

  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in appendix 2; Partial Date Conventions.

6.2. BASELINE

Unless otherwise specified, Baseline is defined as the last non-missing measurement (including unscheduled measurements) taken up to and including Day 1 prior to first administration of study medication. In the case where the last non-missing measurement and the reference start date coincide, collection time, where available, will be compared with the first dose time to determine whether the measurement is pre-baseline or post-baseline. If time is not available or if assessment time coincides with reference start time, the measurement will be considered pre-baseline, but adverse events (AEs), medications and non-medication procedures commencing on the reference start date will be considered post-baseline.

6.3. DERIVED TIMEPOINTS

Derived EOT

For patients that reach their Day 84 visit while still on treatment (also considered the EOT visit), data may not be entered on both Day 84 and EOT eCRF pages. Therefore, a derived EOT assessment will be determined in order that all patients are included in summaries for EOT visit.

Derived EOT visit is defined as the last non-missing measurement (including unscheduled measurements) which started after the first study medication administration up to and including the last study medication administration on the main study phase.

Derived Day 84

Similalry to above, for all efficacy endpoints at Day 84 visit, patients data may not be entered on both Day 84 and EOT eCRF pages. Therefore derived Day 84 efficacy response will be determined for responses entered in the Day 84 window, similar to derived EOT, so that patients will be presented in summary tables at both Derived Day 84 and Derived EOT. .

6.4. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to the derived EOT/EOS value, or best/ worst case value where required (e.g. shift table).

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.5. WINDOWING CONVENTIONS

Visit windows are assigned based on the Protocol SOA are presented in below table.Assigned Visit	SOA day(s)	Study day(s)
V1 (Screening)	-7	-7
V2 (Treatment)	1	1

Visit windows are assigned based on the Protocol SOA are presented in below table.Assigned Visit	SOA day(s)	Study day(s)
V4 (Treatment)	3-5	3 to 5
V6 (Treatment)	6-8	6 to 8
V7 (Treatment)	9-11	9 to 11
V8 (Treatment)	14±2	12 to 16
V9 (Treatment)	17-18	17 to 18
V10 (Treatment)	21±2	19 to 23
V11 (Treatment)	24-25	24 to 25
V12 (Treatment)	28±2	26 to 30
V12a (Treatment)	35±2	33 to 37
V13 (Treatment)	42±3	39 to 45
V13a (Treatment)	49±3	46 to 52
V14 (Treatment)	56±3	53 to 59
V15 (Treatment)	70±3	67 to 73
V16 (Treatment)	84±6	78 to 90
V17 (Treatment)	EOT±3	-
V18 (Treatment)	Follow-up (4 wks after EOT ± 7d)	-
Derived EOT	84±6 or CRF EOT or last assessment done if CRF EOT is missing	78 to 90 or CRF EOT or last assessment done if CRF EOT is missing
Derived Day 84	84±6 or CRF EOT	78 to 90

Visit windows are assigned based on the Protocol SOA are presented in below table.Assigned Visit	SOA day(s)	Study day(s)
Start of Extended Treatment [ET]	Main Study Phase Day 85-91a	-
Extended Treatment	Every 4 weeks ± 7 days	-
End of Extended Treatment	-	-
Follow-up	4 weeks after End of Extended Treatment ± 7 days	-

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.

6.6. STATISTICAL TESTS

The default significance level will be (5%); 95% confidence intervals (CIs) will be presented and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.7. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value
- Percentage change from baseline will be calculated as:
- ([Test Value at Visit X – Baseline Value]/ Baseline Value) × 100

6.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher. Non-compartmental PK parameter calculations will be performed using Phoenix® WinNonlin® 8.0 or higher ([redacted]).

7. STATISTICAL CONSIDERATIONS

7.1. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centres internationally. This is an open-label study, with no randomisation or stratification. Centre pooling will not be carried out for use in analyses for this study.

7.2. MISSING DATA

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.

Missing safety data will not be imputed.

Missing efficacy data will be handled as described in section 16 of this SAP. Missing PK data will be handled as described in section 17 of this SAP.

7.3. MULTIPLE COMPARISONS/ MULTIPLICITY

Not applicable.

7.4. EXAMINATION OF SUBGROUPS

The following subgroups will be presented for DRC-adjudicated overall response, Investigator-assessed overall response, and all-cause mortality. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups, therefore this is a descriptive analysis only.

1) DRC-Adjudicated Baseline Disease Category and subcategory (patients may be included in more than one aspergillus subcategory)
    - Lomentospora (Scedosporium) prolificans (LoPro)
    - Scedosporium spp.
    - Aspergillus - All

- Aspergillus - proven
- Aspergillus - probable (IA-LRTD)
- Aspergillus-R*
- Aspergillus-S *
- Aspergillus-unknown *
- Coccidioides
- Other F901318-susceptible fungi [this would include Fusarium, Phaeoacremon, Scopulariopsis,Histoplasmosis, Madurella, Sporothrix etc.]

- *To determine -azole resistance subcategory, consider the Central and Local Lab Microbiology Data for susceptibility result of 4 -azole drugs (itraconazole, voriconazole, posaconazole, isavuconazole) for the isolate;
    - If aspergillus is resistant to all 4 -azole then consider it as resistant
    - If at least one result is resistant then consider it as resistant
    - If all 4 are susceptible then susceptible
    - If no resistant and at least one susceptible then susceptible
    - If Intermediate and results awaitng then Unknown.

  If the patient has a subcategory of "Unknown" using central lab data, or if central lab data was not available, the same criteria will be used to determine -azole resistance subcategory using local microbiology data. The following breakpoints were used to derive susceptibility result for aspergillus tested in the local lab, using MIC reported by the local lab:
    - isavuconazole: resistant if MIC >1 ug/mL, susceptible if MIC <=1 ug/mL
    - itraconazole: resistant if MIC >1 ug/mL, susceptible if MIC <=1 ug/mL
    - posaconazole: resistant if MIC > 0.5 ug/mL , susceptible if MIC <=0.5 ug/mL
    - voriconazole: resistant if MIC > 1 ug/mL, susceptible if MIC <=1 ug/mL
    - If local MIC test is not available, a positive TR34/L98H test result would also indicate

the isolate would be considered as resistant.

2) Prior antifungal therapy response

- Active (uncontrolled)
- Active (stable)
- Improved
- No therapy/Too brief

If the investigator has entered more than one response for prior antifungal therapy per patient, the worst outcome will be used (i.e. worst=refractory/failing,then stable/persistent, unable to judge, partial, complete)

3) Immunosuppression status

Each subject will be assigned one of 3 categories for immunosuppression status, based upon their underlying disease as completed by the Investigator at time of subject enrolment. Categories will be assigned as follows:

- Highly immunosuppressed will include subjects who have haematological malignancies or have received an haematopoietic stem cell transplantation.
- Moderately immunosuppressed will include subjects who either have immunological disorders (such as AIDS, chronic granulomatous disease and cystic fibrosis) or non-haematological malignancies or who have undergone solid organ transplant
- Low/no immunosuppression will include patients with any other underlying diseases and patients who are immunocompetent.

The immunosuppression category will be assigned as above by manual medical review of underlying disease terms prior to database lock, with appropriate documentation.

A second variant of immune status subgroup using two levels will to also be derived from the above:

- Low/No immunosuppresion
- Moderate + High immunosuppression

4) Duration of prior antifungal therapy

Due to potential inconsistency of the investigator-entered categories in eCRF variable, duration of prior antifungal

therapy (for systemic antifungal therapy received <=14 days before first dose of study drug) will be calculated using start/stop date of antifungal therapy;

For any systemic antifungal therapy received <=14 days before first dose, calculate total duration of exposure for the patient (i.e. stop date – start date + 1 for each antifungal therapy, and sum up total cumulative duration for the patient adding together exposure if more than one relevant antifungal or if antifungals overlap).

Patients will be assigned to subgroup category based on total cumulative duration;

- No prior antifungal therapy 2 weeks prior to study
- 1-7 days
- 8-14 days
- 15-28 days
- 29-90 days
- 91-180 days
- >180 days

Duration category of prior antifungal therapy entered into the eCRF by the investigator is available, but categories overlap and may not be accurate. Subgroup levels will be derived using start and stop dates entered into the eCRF for prior therapy.

Duration of prior antifungal therapy – two level

Using the same calculation as the duration of prior antifungal therapy above, patients will be assigned to a two-level subgroup category based on total cumulative duration;

- 0-28 days
- >28 days

Patients with no prior therapy will be included in the first level of the categories as "0 days".

5) Malignancy type

Malignancy status will be derived for each patient based on primary underlying disease type entered into the eCRF,

and medical review of malignancy type.;

- Haem-malignancy
- Non haem-malignancy
- No malignancy
- Not applicable

6) Neutropenia status

- Neutropenia at screening
- No neutropenia.

Patients who have neutropenia onset date within 28 days prior to first dosing (instead of any onset date prior to treatment start date) date and still ongoing at screening/baseline (i.e. not resolved prior to first dose date) will be categorised as "Neutropenia at screening", otherwise patients will be categorised as "No neutropenia".

7) Reason for Limited Treatment Options

Reason for Limited Treatment Options will be analysed as a 4-level variable for the subgroup analysis, by grouping the criteria for meeting limited alternative treatment options described in the Study Synopsis as follows:

- Known or predicted resistance to all licensed agents (including Known or predicted Resistance, Need oral – azole and -azole resistance is known, Need oral – azole and -azole resistance predicted by PCR, Need oral – azole and -azole resistance is predicted epidemiologically)
- Failure of available therapy (including Failure of available therapy, Inability to produce therapeutic drug levels, MM Approval.
- Intolerance to available therapy (including Intolerance to available therapy)
- Inability to manage DDIs (including Inability to manage DDIs, Need oral -azole Unmanageable azole DDI)

8. Output Presentations

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by [redacted] Biostatistics. Minor modifications may be made to tables, figures, and listings to accommodate the data.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study.

9.1. DISPOSITION

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

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

The number of patients enrolled for each centre and country will be summarised (n and %).

The number of patients included in each analysis set will be summarised. The decision to exclude patients from any of the analysis sets will be finalised at a DR meeting with the Sponsor prior to final database lock. Such excluded patients will be listed and a summary of the main reason(s) for exclusion will be provided. Reason(s) for exclusion can be protocol deviations or other factors that may affect the efficacy outcome or treatment of the patient.

Inclusion/exclusion criteria exceptions, i.e. those patients who met exclusion criteria or who did not meet inclusion criteria but were included in the study and received treatment, will be listed.

All patients (including patient number and site number) whose trial participation was impacted by COVID-19 will be presented in a listing, describing the particular impact.

The number of patients entering the extended treatment phase after completing main study phase, and those not entering the extended treatment phase will be summarised.

The above summaries and listings will be presented for the ENR set.

9.2. PROTOCOL DEVIATIONS

- Protocol deviations identified during the conduct of the study will be captured in the CTMS PD log.
- The CTMS PD log will be used as provided. No additional deviations are to be programmed on the statistical database to be reconciled with the CTMS PD log.
- Major/critical protocol deviations as collected during the conduct of the study and as authorised prior to final database lock will be summarised by type and severity; and a by patient listing with the specific details for all protocol deviations will be provided. The summaries and listings will be presented for the ITT set.
- All protocol deviations relating to COVID-19 will in addition be summarised by type and severity, and a by patient listing with the specific details will be provided.
- Severity of protocol Deviations:
    - Critical: Deviation from protocol related procedures that threaten integrity of data, adversely affect patients and/or could invalidate acceptability of a study (or part of it). Such deviations require immediate action.
    - Major: Deviation from protocol related procedures that could affect integrity of the data or adversely affect patients. Such deviation requires timely action.
    - Minor: Deviations from accepted procedures that will not adversely affect patient/data but should be dealt with appropriately.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT and mITT populations.

No statistical testing will be carried out for demographic or other baseline characteristics.

Descriptive statistics and listings for the following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of informed consent
- Age (years) Categories

- <18 years
- >=18 - <65 years
- ≥65 yearsGender at birth

- Race
- Ethnicity
- Patient's hospitalisation status at screening
- Baseline Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m2) [derived]
- Investigator Baseline Assessment of Fungal Infection
  - IFD under study
  - Categorization of IFD (Probable/Proven), and Method for "Proven"
  - Shipped to Mycology or Cocci Serology Central Lab (Yes/No)
  - Reason for limited treatment options
    a) Known or predicted resistance of the infecting isolate to all licensed agents,
    b) Failure of available therapy,
    c) Intolerance to available therapy,
    d) Inability to manage DDIs and alternative licensed agents are either predicted to be ineffective or are contraindicated,
    e) Inability to produce therapeutic drug levels and alternative licensed agents are either predicted to be ineffective or are contraindicated,
    f) An intravenous (IV) only option (e.g. amphotericin) has produced a clinical response, and it is standard practice to switch to an oral azole to complete 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,

iv. An azole would be acceptable therapy, but it is known or predicted that unmanageable DDIs will occur.

g) Other received MM approval.

- Duration (days) from Baseline fungal infection start to first administration of study medication [derived]
- Investigator Baseline Assessment of Additional Fungal Infection
- Additional baseline fungal infection
- 42 (days) from additional Baseline fungal infection start to first administration of study medication [derived]
- Baseline DRC adjudicated disease category
- Second Baseline DRC-Adjudicated Disease Category
- Baseline objective measure of infection activity/ Initial Categorization of IFD (Presented in Separate Table)
  - Host factors
  - Clinical features (Radiology and Bronchoscopy)
  - Mycological criteria
  - Clinical signs, symptoms and physical findings of IFD
    - If a combination of the above objective measures is applicable subgroup will be "Combination of objective measures". Details on objective measures may be found in the patient listing pertaining to Initial categorization of IFD.
  - Site
    - As collected on the Initial Categorization of Invasive Fungal Disease eCRF page, item named Site. If more than one site is applicable, subgroup will be "Multiple sites". Details on these

multiple sites may be found in the patient listing pertaining to Initial categorization of invasive fungal disease.

- Screening Assessment of IFD
  - Radiology findings
  - Mycology findings
- Pre-Study Course for Fungal Infection Under Study (listed)
  - Was qualifying fungal infection a breakthrough infection (fungal infection that occurred while receiving a mould-active antifungal agent)
  - Was specific therapy begun in response to diagnosis of qualifying fungal infection
  - Duration for each antifungal used as specific therapy for qualifying fungal infection and timing relative to start of study drug.
  - Nature of response to prior antifungal therapy at time of enrolment
  - Was surgery carried out as therapeutic modality for this IFD

10.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ [height (m)]^2
- Age (years) = floor of ([date of informed consent-date of birth]/ 365.25)
- If the date of birth is partial, then the date of birth will be imputed as follows for the calculation of age:
  - If only the day is missing, then the 15th day of the month will be used as the day.
  - If the day and month are missing, then the 02 Jul will be used as the day and month (i.e. the 183rd day of the year).
- Duration (months) from event to first administration of study medication = floor of ([date of first administration of study medication – date of event]/ 30.4375)

11. PRIMARY UNDERLYING DISEASE OR CONDITION, INFECTIOUS DISEASE HISTORY AND MEDICAL HISTORY

Primary Underlying Disease or Condition, Infectious Disease History and Medical History descriptive statistics based on the ITT analysis set will be presented.

- Primary Underlying Disease or Condition data will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA).
    - Data captured on the Primary Underlying Disease or Condition page of the eCRF will be presented by System Organ Class (SOC) and Preferred Term (PT).
    - Primary Underlying Disease or Condition data captured are any underlying disease or condition that predisposes a patient to IFD.
    - If more than one primary underlying disease or condition is applicable, subgroup will be "Multiple primary underlying diseases or conditions". Details on these multiple primary underlying diseases or conditions may be found in the patient listing pertaining to Primary underlying disease or condition
    - Other variables to be summarised include:
        - Duration (months) from initial diagnosis to first administration of study medication [derived]
        - Malignancy (Remission or Relapse)
        - Duration (months) from remission to first administration of study medication [derived]
        - Duration (months) from relapse to first administration of study medication [derived]
        - Solid organ transplant (Yes/No)
        - Type of organ transplanted
        - Duration (months) from solid organ transplant to first administration of study medication [derived]
        - Bone marrow or other progenitor cell transplant (Yes/No)
        - Type of bone marrow or other progenitor cell transplant
        - Type of cells

- Duration (months) from bone marrow or other progenitor cell transplant to first administration of study medication [derived]
- Current or recent (within the past 3 months) history of graft versus host disease (GVHD)
- Duration (months) from start of GVHD to first administration of study medication [derived]
- Grade of GVHD

- Infectious Disease History will be coded using the most recent version of MedDRA.
  - Data captured on the Infectious Disease History page of the eCRF will be presented by SOC and PT.
  - Infectious Disease History captured are any invasive fungal disease (other than the IFD under study) or any other fungal or viral infection within the 6 months prior to first administration of study medication, or any bacterial infections within 1 month prior to first administration of study medication.
- Medical History will be coded using the most recent version of MedDRA.
  - Medical History conditions captured are any existing clinically significant baseline conditions and/or clinically relevant medical conditions (other than the disease under study) occurring within the 3 months prior to first study medication administration, or any other major medical history occurring at any prior time (no time restriction) with the potential to affect immune status.
  - Data captured on the Medical History page of the eCRF will be presented by SOC and PT.
  - Active disease status at baseline based upon medical review (categories of Improving on prior therapy, Active-Stable, Active-Slowly progressing, Active-Rapidly progressing, Active-Little Prior therapy)

11.1. DERIVATIONS

- Duration (months) from event to first administration of study medication = floor of ([date of first administration of study medication – date of event]/ 30.4375)

12. MEDICATIONS

Concomitant and prior Antifungal Medications will be coded using the most recent version of World Health Organisation Drug Dictionary (WHO-DD) and descriptive statistics by ATC level 4 for all concomitant medications

and antifungal concomitant medications based on the ITT analysis set will be presented.

See appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant or post the medication will be classified by the worst case; i.e. concomitant. A medication may be classed as both 'prior' and 'concomitant'.

- 'Prior' medications are medications which were started prior to the first dose of study medication.
- 'Concomitant' medications are medications which were:

started prior to, on or after the first dose of study medication but prior to last dose of study medication,

AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.

- 'Post' medications are medications started after the last dose of study medication (to be listed only).
- Therapeutic drug monitoring data on medications resulting in dose adjustments will be listed.
- Concomitant antifungal usage (Yes/No)
  - number of days of concomitant antifungal usage on study
- Summary will be presented by systemic antifungal medication and non-antifungal medications. Systemic antifungals will be confirmed and provided by medical review process.
- Plot for duration of antifungal medications will also be presented.

12.1. DERIVATIONS

- Duration of antifungal medications (days) = stop date – start date + 1 for each antifungal therapy.

See appendix 2 for handling of partial dates for medications. In Case of missing stop date, duration of antifungal derivation should be performed as follows:

- For Prior or concomitant medications, if stop date is missing, use main phase treatment end date as stop date . If the main phase treatment end date is missing then use last known alive date as stop date.

13. NON-MEDICATION PROCEDURES

Non-medication procedures will be presented for the ITT population by SOC and PT and coded using the most recent

version of MedDRA.

See appendix 2 for handling of partial dates for non-medication procedures. In the case where it is not possible to define a procedure as prior, concomitant or post, the procedure will be classified by the worst case; i.e. concomitant.

- 'Prior' non-medication procedures are procedures which were started prior to the first dose of study medication.
- 'Concomitant' non-medication procedures are procedures which were:

started prior to, on or after the first dose of study medication but prior to last dose of study medication,

AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.

- 'Post' non-medication procedures are procedures which were started after the last dose of study medication.

14. STUDY MEDICATION EXPOSURE

Exposure to study medication in days will be presented for the SAF.

The date of first study medication administration will be taken from the start date and time of administration for dose number 1 on the Exposure eCRF page. The date of last study medication for the main study phase will be the stop date and time of administration for last dose on the Exposure eCRF page that is stopped priorr to the main study phase end.. The date of last study medication for the extended treatment phase will be the stop date and time of administration for last dose on the Exposure eCRF page that is stopped prior to the extended treatment phase end..

Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

A summary table for duration of exposure by baseline DRC Adjudicated category, overall, and dose type(overall, fixed dose, adjusted dose) will be presented.

Duration of Exposure will also be presented for the below categories:

For Main study phase:

≤ 42 days
> 42 days to ≤ 84 days
>84 days

For Extended treatment phase:

≤ 42 days
> 42 days to ≤ 84 days
> 84 days to ≤ 180 days
> 180 days to ≤365 days
> 365 days

Waterfall plot for duration of exposure by baseline DRC-adjudicated disease category, dose type and overall will be presented.

14.1. DERIVATIONS

Duration of exposure (days) up to end of main study phase = date of last study medication administration for the main study phase – date of first study medication administration + 1.

Duration of exposure (days) up to end of extended treatment phase = date of last study medication administration for the extended treatment phase – date of first study medication administration + 1.

15. MAIN STUDY MEDICATION COMPLIANCE

Overall compliance to main study medication will be presented in the form of listing for the SAF.

15.1. DERIVATIONS

Overall compliance to main study medication—based on the drug accountability and exposure data—will be calculated as the actual number of tablets taken (prescribed number of tablets as recorded on exposure eCRF – total number of missed tablets) divided by the prescribed number of tablets expressed as a percentage.

Up to and including protocol amendment 4 patients will receive a loading regimen of approximately 4 mg/kg of F901318 divided into two or three doses (12 or 8 hours apart respectively), followed by a maintenance regimen of approximately 2.5 mg/kg/day divided into two or three doses from Day 2 onwards. Based upon emerging data from studies in healthy volunteers, the recommended dose regimen may be revised to total daily dosages of up to 300 mg

divided into two or three doses.

From protocol amendment 6 onwards patients will receive a one-day oral loading dose of 150 mg bid (dosed 12 ± 1 hours apart) followed by a maintenance dose regimen of 90 mg bid (dosed 12 ± 1 hours apart) from Day 2 onwards. 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.

Due to the dose changing nature of this study, prescribed number of tablets will be calculated from the Exposure eCRF page as follows:

[(Dose number 1's End date and time of study medication administration – Dose number 1's Start date and time of study medication administration + 1) × Dose number 1's Total Daily Dose] + [(Dose number 2's End date and time of study medication administration – Dose number 2's Start date and time of study medication administration + 1) × Dose number 2's Total Daily Dose]

+ … +

[(Dose number n's End date and time of study medication administration – Dose number n's Start date and time of study medication administration + 1) × Dose number n's Total Daily Dose],

where n is the largest dose number recorded on the Exposure eCRF page with End date of study medication administration equal to the date of last study medication for the main study phase. <<divide by 30 (30mg per tablet)>>

Total number of missed tablets will be calculated as follows:

Sum of number of tablets missed, as entered on the Drug Accountability eCRF page for the main study phase.

Overall compliance to main study medication will be calculated as follows:

$$\frac{\text{Prescribed number of tablets} - \text{Total number of missed tablets}}{\text{Prescribed number of tablets}} \times 100$$

16. EFFICACY OUTCOMES

For each efficacy variable, descriptive statistics summarising the data overall and by Baseline DRC-adjudicated disease category will be presented. Additional statistical analyses for the efficacy variables including the subgroup analyses are described below. A list of the subgroups assessed is given in section 7.4.

16.1. PRIMARY EFFICACY

16.1.1. PRIMARY EFFICACY VARIABLE & DERIVATIONS

The primary efficacy variable 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 collected in a separate DRC adjudicated outcome database.

Table A presents the criteria for invasive fungal disease assessment of overall response.

Table A: Criteria for IFD assessment of overall response

Overall Response	Criteria
Success-Complete*:	• Clinical: Meets Criteria for Resolution Complete; • Radiological (if assessed): Shows resolution of radiological abnormalities (≥90% response); • Mycological: Meets criteria for presumed or documented eradication.
Success-Partial*:	• Clinical: Meets Criteria for Resolution-Complete or Resolution-Partial; • Radiological: Shows resolution or improvement of radiological abnormalities (at least 25% response); • 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); OR • Radiological (if assessed): Shows no evidence of progression OR < 25% improvement of radiological abnormalities; OR • 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); OR • Radiological: Worsening or new radiological abnormalities; OR • 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.The rules for Failure are tested next and Failure is assigned if any of its rules are met. The rules for Stable are tested last.

Number and % of patients will be summarised for the 4 categories shown in Table A. N and % will also be summarised for the 3 categories of Success (Success-Complete, Success-Partial), Stable disease (Failure-Stable) and Failure (Failure-Progression, Death, and those patients for whom data at Day 42 cannot be collected or who are considered not evaluable at Day 42).

For statistical primary analysis of overall response rate, values will be assigned to the DRC-adjudicated overall response as follows:

- Success (Success-Complete, Success-Partial),
- Failure (Failure-Stable, Failure-Progression, Death, and those patients for whom data at Day 42 cannot be collected or who are considered not evaluable at Day 42). Patients withdrawn from study medication 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; these patients will be considered as failures at all subsequent timepoints.

As a key important analysis, patients with a stable disease outcome will be considered a success,. i.e. assigning the DRC adjudicated response to categories as follows.

- Success (Success-Complete, Success-Partial, Failure-Stable)
- Failure (Failure-Progression, Death, and those patients for whom data at Day 42 cannot be collected or who are considered not evaluable at Day 42)

This alternative classification, where stable disease outcome can be considered a successful response in the timeframe of this evaluation, is an important analysis due to the nature of this challenging patient population for whom other therapies have already failed.

16.1.2. Missing Data Methods for Primary Efficacy Variable

Patients with a missing DRC-adjudicated overall response at Day 42 will be considered as failures.

Note: All mITT patients will be counted in the denominator of the %/ rate calculation at every visit through Day 84,

even if they discontinue early.

16.1.3. Primary Analysis of Primary Efficacy Variable

The primary objective of this study is to describe the DRC-adjudicated efficacy of F901318 as treatment for infections due to resistant fungi in patients lacking suitable alternative treatment options. More specifically, the primary efficacy analysis will focus on the DRC-adjudicated efficacy in terms of DRC-adjudicated overall response at Day 42.

The primary efficacy analysis will be performed for the mITT population.

Based on the DRC-adjudicated overall response categorized as success or failure (as defined above in Section 16.1.1), a response rate will be calculated for the proportion of successes. A 95% exact Clopper-Pearson CI for the single binomial proportion (Clopper & Pearson, 1934) will be calculated. An analysis comparing the 95% CI for the overall response rate with an estimated historical response rate (and 95% CI) will be presented in a separate report outside of the CSR. Corresponding estimated historical response rates in relevant control populations will be assessed using analyses of available clinical databases, and presented in a similar manner as the calculated F901318/0032 study response rate, outside of the CSR.

In addition, all DRC-adjudicated data will be summarised descriptively and listed.

16.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary efficacy analysis will be repeated for the PPAS.

Additionally, a sensitivity analysis of modified overall response will be performed for the mITT population where success will be defined as follows:

Modified Overall Response	Criteria
Success :	• Clinical: Meets Criteria for Resolution-Complete or Resolution-Partial; • Radiological (if assessed): Shows no change or improvement of radiological abnormalities (≥0% response); • Mycological: Meets criteria for presumed or documented eradication.

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 Modified Overall Response as Success.

Similar to the primary analysis, a response rate will be calculated for the proportion of successes. A 95% exact Clopper-Pearson CI for the single binomial proportion will be calculated.

16.1.5. SECONDARY EFFICACY VARIABLES & DERIVATIONS

16.1.5.1. DRC-adjudicated overall response at Day 7, Day 14, Day 28, main study phase EOT, Day 84, and 4-week follow-up

The text on the description and derivations as set out for the primary efficacy variable applies for this secondary efficacy variable.

For the 4-week follow-up visit, only patients who did not enrol in the extension treatment phase will be considered.

16.1.5.2. Investigator-assessed overall response at Day 7, Day 14, Day 28, Day 42, main study phase EOT, Day 84, and 4-week follow-up

A secondary efficacy variable is the Investigator-assessed overall response at Day 7, Day 14, Day 28, Day 42, main study phase EOT, Day 84, and 4-week follow-up, as determined by the Investigator using all available assessment results including clinical, mycological and radiological results.

Investigator-assessed overall response is collected on the Investigator's diagnostic and response assessment eCRF page.

Refer to Table A for the criteria for invasive fungal disease assessment of overall response. Number and % of patients will be summarised for these categories.

N and % will also be summarised for the 3 categories of Success (Success-Complete, Success-Partial), Stable disease (Failure-Stable) and Failure (Failure-Progression, Death, and those patients for whom data at Day 42 cannot be collected or who are considered not evaluable at Day 42).

For statistical analysis of response rate, values will be assigned to the Investigator-assessed overall response as follows:

- Success (Success-Complete, Success-Partial),
- Failure (Failure-Stable, Failure-Progression, Death, and those patients for whom data at the specific visit cannot be collected or who are considered not evaluable at the specific visit).

Patients withdrawn from study medication 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; these patients will be considered as failures at all subsequent timepoints.

Similarly to the primary endpoint, a important analysis will be performed in which a stable disease outcome will be considered a success, i.e. assigning the Investigator response to categories as follows;

- Success (Success-Complete, Success-Partial, Failure-Stable)
- Failure (Failure-Progression, Death, and missing/not evaluable).

For the 4-week follow-up visit, only patients who did not enrol in the extension treatment phase will be considered.

16.1.5.3. DRC-adjudicated and Investigator-assessed clinical response at Day 7, Day 14, Day 28, Day 42, main study phase EOT, Day 84, and 4-week follow-up

Other secondary efficacy variables include the DRC-adjudicated and Investigator-assessed clinical response at Day 7, Day 14, Day 28, Day 42, main study phase EOT, Day 84, and 4-week follow-up.

DRC-adjudicated clinical response is determined by an independent DRC and collected in a separate DRC adjudicated outcome database.

Investigator-assessed clinical response is collected on the Investigator's diagnostic and response assessment eCRF page.

Table B presents the criteria for clinical response.

Table B: Criteria for clinical response

Clinical Response	Criteria
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.
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	Visit and/or assessment of clinical symptoms and physical findings of IFD was not performed

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

For statistical analysis of clinical response rate, values will be assigned to the DRC-adjudicated and Investigator-assessed clinical response as follows:

- Success (Resolution-Complete, Resolution-Partial),
- Failure (Failure-Stable, Failure-Progression, Deaths, and those patients for whom data at the specific visit cannot be collected or who are considered not evaluable at the specific visit).

Similarly to primary analysis, patients with a stable disease outcome will be considered a success,. i.e. assigning the DRC adjudicated response to categories as follows.

- Success (Resolution-Complete, Resolution-Partial, Failure-Stable)
- Failure (Failure-Progression, Death, and those patients for whom data at the specific visit cannot be collected

or who are considered not evaluable at the specific visit)

Patients withdrawn from study medication 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; these patients will be considered as failures at all subsequent timepoints.

For the 4-week follow-up visit, only patients who did not enrol in the extension treatment phase will be considered.

16.1.5.4. 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 follow-up

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 follow-up are secondary efficacy variables.

DRC-adjudicated radiological response is determined by an independent DRC and collected in a separate DRC adjudicated outcome database.

Investigator-assessed radiological response is collected on the Investigator's diagnostic and response assessment eCRF page.

For the 4-week follow-up visit, only patients who did not enrol in the extension treatment phase will be considered.

Table C presents the criteria for radiological response.

Table C: Criteria for radiological response

Radiology Response
≥ 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, EOT, Day 84 or 4-week FU)).

Radiological response will also be presented grouped in categories and presented at output level:

- "Success" if response is ≥ 90% improvement in aggregate (across all lesions if more than one lesion)
- "Improvement" if response is ≥ 50 to < 90% improvement in aggregate (across all lesions if more than one lesion) and ≥ 25% to < 50% improvement in aggregate (across all lesions if more than one lesion)
- "Stable" if response is No change 0%* to < 25 % improvement in aggregate (across all lesions if more than one lesion)
- "Worsening" if response is Worsening* in aggregate (across all lesions if more than one lesion)
- " Death" if death
- "Not Evaluable/Missing" if response is (No signs on radiological images at screening, Results not available, Missing)

16.1.5.5. 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 follow-up

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 follow-up are also secondary efficacy variables.

DRC-adjudicated mycological response is determined by an independent DRC and collected in a separate DRC adjudicated outcome database.

Investigator-assessed mycological response is collected on the Investigator's diagnostic and response assessment eCRF page.

Table D presents the criteria for mycological response.

Table D: Criteria for mycological response

Mycological Response	Criteria
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.
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.

Patients with a mycological evaluation of "No Mycological Follow-up Results Available" and "Not Done" at a specific visit will be assigned an outcome of:

- "Presumed Eradication" if they are a clinical success at the specific visit,
- "Presumed Persistence" if they are deemed a clinical failure, or if the clinical response is missing at the specific visit.
- Patients with missing clinical response are assigned a response of "No mycological or clinical follow-up available".

For statistical analysis of mycological response, values will be assigned to the DRC-adjudicated and Investigator-assessed mycological response as follows:

- Success (Eradication, Presumed Eradication),
- Failure (Persistence, Presumed Persistence, Recurrent/Emergent infections, death or any other response except Eradication or Presumed Eradication).

Patients withdrawn from study medication 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; these patients will be considered as failures at all subsequent timepoints.

For the 4-week follow-up visit, only patients who did not enrol in the extension treatment phase will be considered.

16.1.5.6. All-cause mortality rate at Day 42, main study phase EOT, Day 84, and 4-week follow-up

All-cause mortality rate at Day 42, main study phase EOT, Day 84, and 4-week follow-up is a secondary efficacy variable.

Survival status is captured on the Survival Status eCRF page.

Mortality rate at visit X is calculated as:

$$\frac{\textbf{Number of deaths up to and including visit X}}{\textbf{mITT population}}$$

For the 4-week follow-up visit, only patients who did not enrol in the extension treatment phase will be considered.

16.1.5.7. Patient-reported outcome at Day 42 and Day 84

A secondary efficacy variable is the quality of life (patient-reported outcome) [redacted] based on the EQ-5D-5L questionnaire. Patient-reported outcome is collected on the Health Questionnaire eCRF page.

The EQ-5D-5L health questionnaire is an assessment where the following five qualitative items are evaluated, i.e. does the patient have issues with:

- Mobility
- Personal care
- Usual activities
- Pain/Discomfort
- Anxiety/Depression

Answers to the five qualitative items include:

- None
- Slight
- Moderate
- Severe
- Extreme

The EQ-5D-5L health questionnaire also includes the quantitative item:

- Visual analogue scale (VAS) score, where the scale is numbered from 0 to 100. 100 means the best health the patient can imagine. 0 means the worst health the patient can imagine.

The EQ-5D-5L profile will be converted into a weighted health state utility value, the EQ-5D-5L Index, by applying a US-based value set derived from a standardized protocol developed by the EuroQol Group (Pickard et al). For derivation for EQ-5D-5L index score, please refer Appendix 3 (Reference[4]). The parameter estimate values are presented in table 2. The parameter estimate for each questionnaire response is presented. i.e. Mobility Slight (MO2)= 0.096.

Please note that score for level 1 of each questionnaire item is 0. i.e. MO1=0, SC1=0, UA1=0, PD1=0 & AD1=0.

The overall health index score(HIS) for a patient at visit is derived by subtracting all the estimate values from 1, ie.HIS = 1 - (MOi + SCi + UAi + PDi + ADi), where i=1,2,3,4,5 response score to respective questionnaire.

- If HIS=1 means perfect health.
    - HIS <1 means there is some negative impairment.

Please note that HIS cannot be >1.

16.1.6. Missing Data Methods for Secondary Efficacy Variables

16.1.6.1. DRC-adjudicated and Investigator-assessed overall response, clinical response, radiological response, mycological response

- Patients with a missing overall response at a specific visit will be considered as failures at the visit.

- Patients with a missing clinical response at a specific visit will be considered as failures at the visit.
- In cases where the radiological test was not done, or results are not available, or the test is not applicable/relevant, this information will appear as such in outputs. In cases where the radiological response is missing (and not captured in one of the before mentioned options), it will be indicated as "Missing" in tables.
- Patients with a missing mycological response at a specific visit will be assessed according to criteria in Table D as either presumed eradication (success), presumed persistence or no mycological follow-up results available (failure) at the visit.

Note: All mITT patients will be counted in the denominator of the %/ rate calculation at every visit through Day 84, even if they discontinue early. For mycological response, all patients with mycological evidence at baseline will be counted in the denominator of the %/rate calculation.

16.1.6.2. All-cause mortality rate

If at a visit a patient is reported as having died, then the patient is considered as a death for subsequent visits.

For cases where a death was not reported at a previous visit, and survival status is missing/not done at the specific visit, the survival status will be indicated as "Missing".

16.1.6.3. Patient-reported outcome

Missing results will not be imputed for patient reported outcome and will be indicated as "Missing" in tables.If any questionnaire response is missing then heath index score (HIS) will also be set to be missing for that patient at specific visit.

16.1.7. Analysis of Secondary Efficacy Variables

16.1.7.1. Analysis of DRC-adjudicated and Investigator-assessed overall response

Analyses of these secondary efficacy variables will be similar to the analysis of the primary efficacy variable.

16.1.7.2. Analysis of DRC-adjudicated and Investigator-assessed clinical response

Based on the DRC-adjudicated and Investigator-assessed clinical response categorized as success or failure (as defined above in Section 16.2.1.3), a response rate will be calculated for the proportion of successes. In addition, a 95% exact Clopper-Pearson CI for the single binomial proportion (Clopper & Pearson, 1934) will be calculated.

All DRC-adjudicated clinical response data will be summarised descriptively and listed. Investigator-assessed clinical response data will be summarised descriptively and listed including extended phase data.

Clinical signs and symptoms data, as collected on the Screening Assessment of Clinical Signs and Symptoms and Assessment of Clinical Signs and Symptoms eCRF pages, will be summarised descriptively and listed.

16.1.7.3. Analysis of DRC-adjudicated and Investigator-assessed radiological response

DRC-adjudicated and Investigator-assessed radiological response will be summarised descriptively and listed.

Radiological assessment data, as captured on the Radiologic Assessment eCRF page, and central radiology data, as obtained from the external vendor Bioclinica, will be summarised descriptively and listed.

16.1.7.4. Analysis of DRC-adjudicated and Investigator-assessed mycological response

Based on the DRC-adjudicated and Investigator-assessed mycological response categorized as success or failure (as defined above in Section 16.2.1.5), a response rate will be calculated for the proportion of successes. In addition, a 95% exact Clopper-Pearson CI for the single binomial proportion (Clopper & Pearson, 1934) will be calculated.

Serum galactomannan (GM antigen) will be assessed for all patients with proven or probable IA.Summary table for serum GM will be presented by visits and baseline DRC adjudicated disease categories.Plot of Serum GM(mean+/-SD) by visits and baseline DRC adjudicated disease categories will be presented. Spaghetti plot for serum GM over visits will be presented.

The following data will also be listed:

- Bronchoscopic assessment data, as captured on the Bronchoscopic Assessments eCRF page.
- Other microbiological assessment data, as captured on the Other Microbiological Assessments eCRF page.
- Other mycological (fungal) assessment data, as captured on the Other Mycological (Fungal) Assessments eCRF page.

- Histology/cytology*, as captured on the Histology/Cytology eCRF page.
- Fungal culture data*, as captured on the Fungal Culture eCRF page.
- GM antigen data*, as captured on the GM Antigen – Central, GM Antigen – Central Repeat, and GM Antigen – Local eCRF pages.
- Polymerase Chain Reaction data*, as captured on the PCR – Polymerase Chain Reaction eCRF page.
- Susceptibility Testing data, as captured on the Susceptibility Testing eCRF page.
- Cocci serology local and central data, as captured on the Cocci Serology eCRF page.

*Samples may be shipped to the central general/cocci mycology laboratories, and all data from the central mycology laboratories (general and cocci) will also be listed.

16.1.7.5. Analysis of all-cause mortality rate

Survival status data are collected at Day 42 visit, at main study phase EOT visit, at Day 84 visit, and at the 4-week follow-up visit. Where survival status was not collected at the visit, additional methods of ascertaining survival status will be used including safety reviews conducted by the sponsor and last known contact date using other information collected in the eCRF.

The all-cause mortality rates at Day 42, at main study phase EOT, at Day 84, and at 4-week follow-up will be calculated using the expression described in section 16.2.1.6 for mortality rate at visit X.

In addition, a 95% exact Clopper-Pearson CI for a single binomial proportion (Clopper & Pearson, 1934) will be calculated.

A survival analysis will be performed using the survival status data stratified by baseline DRC-adjudicated disease category. Overall survival is defined as the time from the date of first dose of study drug until death due to any cause in general. Patients not known to have died at the time of data cut-off will be censored at the last date known to be alive on the main study. Overall survival will be presented graphically using the Kaplan-Meier plots. The Kaplan-Meier plots will be truncated when the number of patients at risk is <5, as beyond this point interpretation is problematic due to the large degree of uncertainty in any estimates provided.. The estimated overall survival rates at Day 42, Day 84 and Day 112 will be estimated via the Kaplan-Meier method. The corresponding 95% CI (using the Greenwood formula method of Kalbfleisch and Prentice, 1980) for each estimated overall survival rate will be presented. Also, median overall survival and the corresponding 95% CI (using the method of Brookmeyer and Crowley, 1982 with the log-log transformation) will be summarized. The cumulative number and % of subjects who

died before or during each of the landmark time points Day 42, Day 84 and Day 100 will be presented.

16.1.7.6. Analysis of Patient-reported outcome

Both EQ-5D-5L qualitative and quantitative items will be summarised descriptively and listed for main phase and extended phase data.

In addition, the qualitative items will be presented as shift from baseline to the scheduled visits, and also as shift from baseline to derived EOT. Qualitative items will also be presented by means of a stacked bar chart.

Summary statistics will be presented for the EQ-5D-5L index score at each visit, as well as change from baseline.

17. PHARMACOKINETIC ANALYSIS

The PK parameter calculations will be the responsibility of the clinical pharmacokineticist at IQVIA, Overland Park, Kansas, United States. The concentration summaries, PK parameter summaries, data listings, and associated graphic presentation will be the responsibility of the study biostatistician at IQVIA, Bloemfontein, South Africa.

Scheduled intensive PK day plasma concentrations and PK parameters for olorofim [redacted] (central bioanalytical lab) will be summarized using descriptive statistics, including n, mean, SD, coefficient of variation (CV%), median, minimum, and maximum. geometric mean, and CV% for geometric mean (GeoCV%). For time of maximum concentration (Tmax), only n, median, minimum, and maximum will be provided. If the number of non-missing observations at a time point is fewer than 3, the data at the time point will not be summarized. Scheduled intensive PK day plasma concentrations and PK parameters will be summarised by dosing methodology (adjusted (all), adjusted (BID), adjusted (TID) or fixed dosing) using descriptive statistics, including n, mean, median, 95% CI, minimum and maximum. Intensive PK day PK parameters will also be summarised by concomitant medication (CYP3A4 inhibitors and inducers) demographics (age, sex, race) and underlying condition (immue status, baseline creatinine clearance, GvHD)) using descriptive statistics, including n, mean, median, 95% CI, minimum, and maximum.

In general, scheduled trough data (central bioanalytical lab and regional hub) will be summarised by dosing methodology (adjusted or fixed dosing) and regimen (BID or TID) using descriptive statistics, including including , mean, SD, coefficient of variation (CV%), median, minimum, and maximum, geometric mean, and CV% for geometric mean (GeoCV%). Trough parameters will be summarised by dosing methodology (adjusted (all), adjusted (BID), adjusted (TID) or fixed dosing), concomitant medication (CYP3A4 inhibitors and inducers), demographics (age, sex, race) and underlying condition (immue status, baseline creatinine clearance, GvHD) using descriptive statistics, including n, mean, median, 95% CI, minimum, and maximum.

Concentration data will be reported and analyzed with the same precision as the source regardless of how many significant figures or decimals the data carry. Concentration ratios will be reported to the same precision as source, with no more than three decimal places. Pharmacokinetic parameters and concentration ratios will be rounded for reporting purposes in the by-subject listings, but the unrounded values will be used for the calculation of the summary statistics and in the inferential analyses. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure for data reporting, with the following exceptions:

- Pharmacokinetic parameters directly derived from source data (C_{max}, C_{before}, $Trough_{avg}$, etc.) will be reported and analyzed with the same precision as the source data.
- Pharmacokinetic parameters derived from actual elapsed sample collection times (e.g., T_{max}) will be reported to 2 decimal places.

Reporting of mean, SD, minimum, median, maximum, and geometric mean will follow the same precision of source concentrations or the rounding convention of the individual PK values. The CV% and GeoCV% will always be reported to 1 decimal place.

17.1. PLASMA CONCENTRATION DATA

Samples for trough PK concentration determination are split into two aliquots, with one aliquot shipping to the regional hub for rapid analysis and one aliquot shipping to the central laboratory. Both laboratory results will be listed, and scheduled trough plasma concentration data will be summarised from both central and regional laboratories. Samples for intensive PK day concentration determinations will be sent to the central laboratory only and these data will be used to summarise intensive PK day plasma concentrations and parameter determination/tabulation.

A listing of PK blood sample collection times as well as derived sampling time deviations and concentrations (olorofim from both central and regional labs [redacted] from central lab) will be provided. This listing will include all samples, including unscheduled samples.

The ratio of plasma [redacted] plasma olorofim will be determined at every intensive sampling time, as appropriate, and [redacted] If one result is below the limit of quantitation (BLQ), then BLQ will be treated as 1/2*lower limit of quantitation (LLOQ) for ratio calculations and the results will be flagged in listings as such. If both results are BLQ or one result is missing, a ratio will not be determined.

All plasma concentrations and associated ratios will be summarized by scheduled sampling time using descriptive statistics. These summaries will be presented by dosing type (Adjusted and Fixed dosing type and combined).. Concentrations that are BLQ will be treated as LLOQ/2 for the computation of descriptive statistics.

Trough concentrations will be excluded from descriptive statistics and/or concomitant medication or trough parameters (described below) if the sample is collected more than 1 hour before or more than 15 minutes after its associated dose, , or the time of the previous dose was not collected, or the sample was collected fewer than 5 days after the end of a temporary dose interruption. Otherwise, trough concentrations will be included in calculations and summaries regardless of sampling time deviation.

Concentrations versus time will be presented graphically as follows:

- Spaghetti plots of individual trough olorofim concentrations (scheduled and unscheduled) versus study day presented by dosing type (Adjusted and Fixed) and study phase (main and extended) based on central laboratory and regional laboratory data.
- Box/Whisker plots of trough olorofim concentrations (scheduled and unscheduled) presented by dosing type (Adjusted, Fixed and Combined) and study phase (main and extended) based on central laboratory and regional laboratory data.
- Mean (+SD) scheduled trough olorofim and [redacted] concentrations (central laboratory) versus study day by dosing type (Adjusted or Fixed), dosing regimen (BID and TID) and study phase (main and extended) will be presented on a linear and semi-log scale.
- By-subject olorofim trough concentrations (central lab and regional hub) (y-axis) and total daily dose (presented on a second y-axis) versus study day will be presented will be presented on a linear scale.
- Intensive PK day mean olorofim and [redacted] concentration-time plots by dosing type (Fixed, Adjusted (BID)) and Adjusted (TID) will be presented on a linear scale. Similar concentration-time plots [redacted] intensive PK mean olorofim and [redacted] data will be presented for the Adjusted dosing subjects dosing regimen (BID and TID).
- Box/Whisker plots of selected intensive PK day PK parameters for olorofim presented by dosing type (Adjusted, Fixed and Combined)
- Spaghetti plots of individual intensive PK day olorofim and [redacted] concentration-time profiles will be presented by dosing type (Fixed, Adjusted (BID) and Adjusted (TID))
  By-subject intensive PK day olorofim and [redacted] concentration-time plots on a linear scale, with mealtimes indicated on the x-axis.
  Mean and 95% confidence intervals of selected intensive PK day PK parameters for olorofim presented by concomitant medication, demographic and underlying condition sub groups

17.1.1. CONCOMITANT MEDICATIONS

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Selected olorofim trough parameters will be summarized by concomitant medication group (no/weak inhibitors of CYP2C9 and CYP3A4, moderate inhibitors of CYP2C9 or CYP3A4, strong inhibitors of CYP2C9 or CYP3A4, dual moderate inhibitors of CYP2C9 and CYP3A4, no/weak inducers of CYP3A4, moderate or strong inducers of CYP3A4) provided the medication has been administered to at least three subjects during the main phase of the study. Individual data will be listed for all cases where these concomitant medications are administered during the main phase of the study.

Selecetd olorofim PK parameters will be summarized by concomitant medication group (no/weak inhibitors of CYP2C9 and CYP3A4, moderate inhibitors of CYP2C9 or CYP3A4, strong inhibitors of CYP2C9 or CYP3A4, dual moderate inhibitors of CYP2C9 and CYP3A4, no/weak inducers of CYP3A4, moderate or strong inducers of CYP3A4) provided the medication has been administered to at least three subjects on the intensive PK day. Figures of mean and 95% confidence interval will also be presented graphically for each concomitant medication group. Individual data will be listed for all cases where these concomitant medications are administered on the intensive PK day.

17.1.2. Individual Trough Parameters

The following olorofim trough parameters will be calculated for each patient for the main and extended study phases based on central laboratory data. All trough concentrations, even unscheduled, will be included in these calculations, with the exceptions of the exclusions mentioned above.

Troughmax	Maximum trough concentration
Troughmin	Minimum trough concentration
Troughmed	Median trough concentration
Troughavg	Average trough concentration

These trough parameters will be listed and summarized using descriptive statistics by dosing type (Adjusted, fixed, and all combined) and study phase (main and extended), as appropriate. In addition, trough parameters will be summarized by demographics (sex, age, race) and underlying condition (immune status, baseline creatinine clearance, GvHD) for the main study phase only.

17.2. Intensive Pharmacokinetic Parameters

Subjects with partial data will be evaluated on a case by case basis to determine if they have sufficient data for PK

parameter analysis.

For PK parameter calculations, if the end of tau concentration is missing, the predose result will be substituted for the missing end of tau sample. If the presdose sample is missing the end of tau concentration will be substituted for the missing predose sample). Any BLQ concentration will be assigned a value of ½ LLOQ

The following plasma PK parameters will be estimated for olorofim and [redacted] after intensive PK sampling on [redacted] by non-compartmental methods using actual elapsed time from dosing (rounded to 2 decimal places). A minimum of 3 quantifiable concentration-time data points will be required for calculation of PK parameters..

C_{max}	Maximum concentration obtained directly from the observed concentration versus time data.
C_{max}/D	Dose-normalized C_{max} (µg/mL/mg), calculated by dividing C_{max} by the dose of olorofim.
T_{max}	Time of maximum concentration, obtained directly from the observed concentration versus time data.
C_{min}	Minimum concentration after multiple dosing, obtained directly from the observed concentration versus time data.
C_{min}/D	Dose-normalized C_{min} (µg/mL/mg), calculated by dividing C_{min} by the dose of olorofim.
$C_{(0)}$	Predose concentration on intensive PK day
$C_{(0)}/ C_{min}$	Ratio of $C_{(0)}/ C_{min}$
T_{min}	Time of minimum concentration after multiple dosing, obtained directly from the observed concentration versus time data.
C_{avg}	Average concentration over the dosing interval tau, calculated as $AUC_{(0\text{-}tau)}$ divided by the dosing interval, tau. Actual elapsed time at the end of the dosing interval will be used for the calculation.
C_{avg}/D	Dose-normalized C_{avg} (µg/mL/mg), calculated by dividing C_{avg} by the dose of olorofim.
$AUC_{0\text{-}tau}$	Area under the concentration-time curve during a dosing interval "tau". Actual elapsed time at the end of the dosing interval will be used for the calculation. If actual time is not within 80% to 120% of the dosing interval, or if more than 25% of scheduled sampling occasions over the dosing interval are missing, $AUC_{(0\text{-}tau)}$ will not be reported.
$AUC_{0\text{-}tau}/D$	Dose-normalized $AUC_{0\text{-}tau}$ (µg*h/mL/mg), calculated by dividing $AUC_{0\text{-}tau}$ by the

	dose of olorofim.
AUC_{0-24}	AUC_{0-tau} multiplied by a factor of 2 and 3 for BID and TID dosing, respectively.
AUC_{0-24}/D	Dose-normalized AUC_{0-24} (µg*h/mL/mg), calculated by dividing AUC_{0-24} by the dose of olorofim.
CL/F	Apparent systemic clearance after extravascular dosing, calculated as dose divided by AUC_{0-tau}. Calculated for olorofim only.
MRC_{max}	Ratio of metabolite [redacted] C_{max} to parent olorofim C_{max}, and adjusted for the ratio of molecular weights (498/514).
$MRAUC_{0-tau}$	Ratio of metabolite [redacted] AUC_{0-tau} to parent olorofim AUC_{0-tau}, and adjusted for the ratio of molecular weights (498/514).

Area under the concentration-time curve will be calculated by linear up/log down trapezoidal summation. No dose adjustment is necessary for the calculation of the selected parameters. Pharmacokinetic parameters will be summarized using descriptive statistics for each analyte and dosing type (adjusted, fixed and combined). Summaries of olorofim PK parameters by demographics (sex, age, race) and underlying condition (immune status, baseline creatinine clearance, GvHD)will also be produced. A subject listing of individual PK parameters will be provided. Box/Whisker plots of individual intensive PK day Cmax, Cmin, and AUC0-tau, presented by analyte and dosing type, will be provided, together with mean and 95% confidence intervals for selected olorofim PK paramaters presented by demographics and underlying condition.

[redacted]

18. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the SAF.

18.1. ADVERSE EVENTS

Adverse Events will be coded using the most recent version of MedDRA.

- TEAEs will be presented by phase; TEAEs occurring in the main phase, TEAE's occurring in the extended phase, and TEAEs occurring in main or extended phase.

- TEAEs occurring in the main phase are defined as any AE which started or worsened on or after the first dose of main phase study treatment up to and including the post-treatment follow-up for the main phase.
- TEAEs occurring in the extended phase are defined as any AE which started or worsened on or after the first dose of extended phase study treatment up to and including the post-treatment follow-up for the extended phase. Note that if an AE occurred during the main phase, but worsened during the extended phase, the event qualifies as occurring in both main and extended phase. TEAEs occurring in main or extended phase are defined as any AE which started or worsened on or after the first dose of main phase study treatment up to and including the post-treatment follow-up for the extended phase.

See appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case; i.e. treatment-emergent.

A table listing the TEAEs with overall frequency >3% by preferred term in decreasing order of number of subjects with at least one TEAE in the preferred term will be presented.

Listings will include TEAEs and Non-TEAEs.

18.1.1. ALL TEAEs

Incidence of TEAEs will be presented by SOC and PT and broken down further by maximum severity and relationship to study treatment.

18.1.1.1. Severity

Severity is classed as mild (grade 1)/ moderate (grade 2)/ severe (grades 3, 4 and 5) (increasing severity using Common Terminology Criteria for Adverse Events [CTCAE] grading). TEAEs starting after the first dose of study treatment with a missing severity will be classified as severe. If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worstcase severity will be used in the corresponding severity summaries.

18.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as "unrelated", "unlikely related", "possibly related", "probably related", or "unknown" (increasing severity of relationship). A "related" TEAE is defined as a TEAE with a relationship to study treatment as *"possibly related" or "probably related"*. TEAEs with a missing or "unknown" relationship to study treatment will be regarded as *"probably related"* to study treatment. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study treatment will be used in

the corresponding relationship summaries.

18.1.2. TEAEs Leading to Discontinuation of Study Treatment

TEAEs leading to permanent discontinuation of study treatment will be identified by "Action taken with study treatment" on the AE eCRF page indicated as "Drug withdrawal".

For TEAEs leading to discontinuation of study treatment, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

18.1.3. TEAEs Leading to Study Withdrawal

TEAEs leading to premature study withdrawal will be identified by "Did the AE cause the patient to discontinue from the study" on the AE eCRF page indicated as "Yes".

For TEAEs leading to premature study withdrawal, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

18.1.4. Serious Adverse Events (Including Deaths)

Serious adverse events (SAEs) are those events recorded as "Serious" on the AE page of the eCRF. A summary of serious TEAEs by SOC and PT, and a summary of serious TEAEs by SOC, PT and relationship to study treatment, will be prepared.

18.1.5. Adverse Events Leading to Death

TEAEs leading to death are those events which are recorded as "Fatal" on the AE page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared.

18.1.6. Adverse Events Of Special Interest

Adverse Events of Special Interest (AESIs) are to have "Yes" recorded as the response to the question "Does this event meet the definition of an Adverse Event of Special Interest" on the AE eCRF page.

The following events are classified as AESIs:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

The CTCAE Grade definitions used for this study's AESIs are given in Table 6 of protocol amendment 6.

AESIs are entered into the database by centres, and [redacted] Biostatistics will not programmatically verify the AEs meeting CTCAE criteria.

Summaries of Treatment emergent AESI incidence rates (number and percentage of patients) by AESI Category, SOC, PT (as determined by the investigator) will be prepared.

Summaries of Treatment emergent AESI incidence rates (number and percentage of patients) by AESI Category, SOC, PT and relationship (as determined by the investigator) will be prepared.

A summary of [redacted] by AESI Category, SOC, PT and relationship (as determined by the HAC) will be presented separately.

AESIs leading to death are those AESI events which are recorded as "Fatal" on the AE page of the eCRF.

Summaries of Treatment emergent AESI incidence rates leading to death (number and percentage of patients) by AESI Category, SOC, PT and relationship (as determined by the investigator) will be prepared.

AESIs leading to permanent discontinuation of study treatment will be identified by "Action taken with study treatment" on the AE eCRF page indicated as "Drug withdrawal".

Treatment emergent AESIs leading to permanent discontinuation of study treatment will be summarised by AESI Category, SOC and PT (as determined by the investigator).

AESIs leading to temporary discontinuation of study treatment will be identified by "Action taken with study treatment" on the AE eCRF page indicated as "Drug interrupted".

Treatment emergent AESIs leading to temporary discontinuation of study treatment will also be summarised by AESI Category, SOC and PT.

Duration of study treatment discontinuation will be listed.

Histogram for number of [redacted] events by duration of Olorofimtreatment(in Weeks) will be plotted.

18.1.7. CTC Grading for Adverse Events

AEs will be graded using the Common Toxicity grading (CTC) system as defined in:

Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

CTC grades are assigned by the study centres and will not be programmatically verified by IQVIA Biostatistics.

18.1.8. TEAEs Leading to Dose Adjustments

TEAEs leading to dose adjustments will be identified by using the "Action taken with study treatment" question on the AE eCRF page, to which the answer is "Dose increased" or "Dose reduced".

For TEAEs leading to dose adjustments, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

18.2. LABORATORY EVALUATIONS

Haematology and Serum Chemistry results from both the local and central laboratories will be included in the outputs for the study report. If both a local laboratory result and the central laboratory result exist for a visit, the central laboratory results of the two will be used in the summary tables and figures. All local and central laboratory results will be listed.

Urinalysis results from the local laboratory will be included in the outputs for the study report.

A list of laboratory assessments to be included in the outputs is included in protocol amendment 6, Table 7.

Presentations will use SI Units. Central laboratory data will be provided to IQVIA Biostatistics in SI Units. IQVIA Biostatistics will convert local laboratory results to display in SI Units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for scheduled Haematology and Chemistry laboratory data:

- Table and box-and-whiskers plot of actual and change from baseline values descriptive statistics by visit (for quantitative measurements)
- Incidence of abnormal values according to normal range criteria
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements)
- Incidence of predefined treatment-emergent abnormalities, as defined by CTCAE criteria
- Shift from baseline according to CTC grading system
- Listing of Haematology and Chemistry laboratory data
- [redacted] as described in section 18.2.4.
- The following will be presented in data listings:
- Urinalysis data
- Hepatologist review data

- Neutropenia status and absolute neutrophil count local laboratory results confirming neutropenia status

18.2.1. Laboratory Specific Derivations

Cockcroft-Gault (CG) formula for Creatinine clearance derivation:

Formula for male: CrCl = [(140-age in years) x (Weight in kg)] / (72 x Cr)

Formula for female: CrCl = [(140-age in years) x (Weight in kg) x 0.85] / (72 x Cr)

Cr (serum creatinine) = mg/dL [need to make sure Cr is provided on mg/dL (and if not a conversion will be needed)] as specified.

18.2.2. Weight collected at each visit and age based on CRF.Laboratory Reference Ranges

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

18.2.3. CTC Grading for Laboratory Data

Laboratory measurements will be graded using the Common Toxicity grading (CTCAE v5.0) system as defined in the following link:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

CTCAE grading that will be used is summarized in the below:

CTCAE Term	Laboratory Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	Hemoglobin (g/L)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Hemoglobin increased	Hemoglobin (g/L)	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-	-
Platelet count decreased	Platelet count (x10E9/L)	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3 ; <25.0 x 10e9 /L	-
Disseminated intravascular coagulation	Platelet count (x10E9/L)	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
White blood cell (WBC) decreased	WBC (x 10E9/L)	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-

CTCAE Term	Laboratory Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Leukocytosis	WBC (x 10E9/L)	-	-	>100,000/mm 3	Clinical manifestation s of leucostasis; urgent intervention indicated	Death
Neutrophils count decreased	Absolute neutrophils count (x 10E9/L)	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Hypernatremia	Sodium (mmol/L)	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalizatio n indicated	>160 mmol/L; life-threatening consequences	Death
Hyponatremia	Sodium (mmol/L)	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death
Hyperkalemia	Potassium (mmol/L)	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalizatio n indicated	>7.0 mmol/L; life-threatening consequences	Death

CTCAE Term	Laboratory Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hypokalemia	Potassium (mmol/L)	≥ 3.0 mmol/L – < LLN	n/a	≥ 2.5 - < 3.0 mmol/L	< 2.5 mmol/L	n/a
Hypercalcemia	Calcium (mmol/L)	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Hypocalcemia	Calcium (mmol/L)	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death

CTCAE Term	Laboratory Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hyperglycemia	Glucose (mmol/L)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypoglycemia	Glucose (mmol/L)	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Glucose intolerance	Glucose (mmol/L)	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Severe symptoms; insulin indicated	Life-threatening consequences; urgent intervention indicated	Death
Creatinine increased	Creatinine (µmol/L)	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-

CTCAE Term	Laboratory Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Alkaline phosphatase (ALP) increased	ALP (U/L)	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Alanine aminotransferase (ALT) increased	ALT (U/L)	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Aspartate transaminase (AST) increased	AST (U/L)	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-

CTCAE Term	Laboratory Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Blood bilirubin increased	Total bilirubin (µmol/L)	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-
CPK increased	Creatine phosphokinase	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Creatinine increased	Creatinine	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Gamma glutamyl transferase (GGT) increased	GGT (U/L)	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Hypoalbuminemia	Albumin (g/L)	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death

CTCAE Term	Laboratory Test	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Activated partial thromboplastin time prolonged	Prothrombin time and activated Partial Thromboplastin Time	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	-	-
Hepatic failure		-	-	Asterixis; mild encephalopathy; drug-induced liver injury (DILI); limiting self care ADL	Life-threatening consequences; moderate to severe encephalopathy; coma	Death
INR increased	Prothrombin time and activated Partial Thromboplastin Time	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-	-

Predefined treatment-emergent abnormalities, 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 one post-dose value recorded.
- If a CTCAE criterion does not consider change from baseline, to be evaluable the patient need only have one 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.

18.2.4.

[redacted]

18.3. ECG EVALUATIONS

Results for 12-lead electrocardiograms (ECGs) will be included in the reporting of this study.

The following ECG parameters will be reported for this study:

- Heart Rate (bpm)
- PQ Interval (PR) (msec)
- RR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF – Fridericia's formula (msec)
- Overall assessment of ECG (Investigator's judgment):

Normal

Abnormal, Not Clinically Significant (ANCS)

Abnormal, Clinically Significant (ACS)

The following summaries will be provided for ECG local and central overread data:

- Table and box-and-whiskers plot of actual and change from baseline value descriptive statistics by visit (for quantitative measurements)
- Shift from baseline in overall assessment of ECG (Investigator's judgment)
- Incidence of treatment-emergent markedly abnormal criteria
- Listing of ECG data

18.3.1. ECG Specific Derivations

Not applicable.

18.3.2. ECG Categories

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined criteria:

- Absolute values for QTcF will be classified as:
  - > 450 msec
  - > 480 msec
  - > 500 msec
- Change from Baseline for QTcF will be classified as:
  - > 30 msec increase from Baseline
  - > 60 msec increase from Baseline

Predefined treatment-emergent categories will be presented in tables where the incidence rate will be based on the total number of patients 'at risk', for example:

- If a criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least one post-dose value recorded.

- If a criterion does not consider change from baseline, to be evaluable the patient need only have one post-dose value recorded.
- Central overreads of ECG data began part way through the study. Summaries of QTcF, incidence of prolongation and spaghetti plot for absolute QTcF over time will be provided for ECG prospective central and retrospective central assessments.

18.4. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Body Temperature (^{o}C)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2) [derived]

The following summaries will be provided for vital signs data:

- Table and box-and-whiskers plot of actual and change from baseline value descriptive statistics by visit
- Incidence of treatment-emergent markedly abnormal values
- Listing of vital signs

18.4.1. VITAL SIGNS SPECIFIC DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ [height (m)]^2
- Body Temperature may be recorded in either ^{o}C or ^{o}F. For summarization purposes, ^{o}F will be

converted to °C as follows:

- Body Temperature in °C = (Body Temperature in °F – 32) × **5/9**
- Height may be recorded in either cm or inch. For summarization purposes inch will be converted to cm as follows:
- Height in cm = Height in inch × 2.54

18.4.2. Vital Signs Markedly Abnormal Criteria

Predefined treatment-emergent abnormalities will be presented in tables where the incidence rate will be based on the total number of patients 'at risk', for example:

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

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Variable (Unit)	Low	High
Systolic Blood Pressure (mmHg)	NA	Hypertension-SBP>=140
Diastolic Blood Pressure (mmHg)	NA	DBP>=80
Pulse rate (BPM)	Sinus bradycardia: <60	Sinus tachycardia: >100 Supraventricular tachycardia: >100 Ventricular tachycardia: >100
Body temperature (˚C)	Hypothermia<=35(grade 2)	Fever >=38 (grade 1)
Weight (kg)	Weight Loss- percentage change from baseline ≤ -5.0 %	Weight Gain- percentage change from baseline ≥ 5.0 %

NA-Not Available.

In the event that a vital sign value does not comply with the criterion for classification as Low or High, the value will be categorised as normal.

18.5. HOSPITALIZATION RECORDS

The following hospitalization records will be reported for this study:

- Event type
- Date of Ward Change, Hospital Admission/Re-admission, Discharge
- Type of Ward or discharge Destination
- Reason for Ward Change, Hospital Admission/Re-admission, Discharge
- Was the Change Associated with the Enrolling Fungal Infection
- Outpatient Healthcare Services
  - Number of outpatient office/clinical visits
  - Number of visits to emergency department that did not lead to hospitalization
  - Number of home care visits provided by medical professionals
  - Type of service

The following summaries will be provided for hospitalization records data:

- Incidence of hospitalization events, types of ward/discharge destinations and types of healthcare services received
- Listing of hospitalization records

18.6. PHYSICAL EXAMINATION

Physical examination findings will only be presented in data listings.

18.7. [redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

18.8. PREGNANCY TEST

Pregnancy test data will only be presented in data listings.

19. [redacted]

[redacted]

20. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Laboratory sample collection information, for example accession number.
- Data resulting from sample shipments made to central laboratories, as captured on the Central Lab Shipment eCRF page.

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, Study Data Tabulation Model (SDTM) and/or Analysis Data Model (ADaM) datasets.

21. REFERENCES

1. Brookmeyer, R., & Crowley, J. (1982). A Confidence Interval for the Median Survival Time. International Biometric Society, 38, 29-41.

2. Clopper, C. J., & Pearson, E. S. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26, 404–413.

3. Kalbfleisch, J. D., & Prentice, R. L. (1980). The Statistical Analysis of Failure Time Data (First ed.). John Wiley & Sons, Inc.

4. VALUE HEALTH. 2019; 22(8):931–941

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

[redacted] OUTPUT CONVENTIONS

Outputs will be presented according to the following:

ABBREVIATIONS

ASCII	American standard code for information interchange file format
CGM	Computer graphics metafile
ODS	Output Delivery System
RTF	Rich text file format

INTRODUCTION

This document applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures. These standards should be used in the absence of customer specific standards.

OUTPUT FILE NAMING CONVENTIONS

File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.

As far as possible, output files should be in RTF format, although .DOC files are also permitted.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('T' for table, 'L' for listing and 'F' for figure). If there is only 1 digit in the number of the table, listing or figure in the place

where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (eg T14_3_01_1.rtf)

PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter for the United States, otherwise A4.
The page orientation should preferably be landscape, but portrait is also permitted.
Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.
The number of columns per page (linesize) should be 145 for A4 and 134 for Letter.
The number of rows per page (pagesize) should be 49 for A4 and 51 for Letter.

FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8.
The font color should be black. No **bolding**, underlining or *italics* should be permitted. Single spacing should be used for all text.
Figures should have a default font of "Times Roman", "Helvetica", or "Courier New".
This can be achieved by using the following options in SAS:

```
goptions
gunit = pct
cback = white
colors = (black)
hby = 2.4
ftext = "TimesRoman"
htext = 2.5
device = cgmof971
gaccess = gsasfile;
filename gsasfile "….cgm";
```

HEADER INFORMATION

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing
- The customer name and protocol number should appear in row 1, left-aligned

- The output identification number should appear in row 2, centered
- The output title should start in row 3, centered
- The output population should appear in row 4, centered. The population should be spelled out in full, e.g. Intention-to-Treat in preference to ITT.
- Row 5 should be a continuous row of underscores ('_') (the number of underscores should equal the linesize)
- Row 6 should be a blank line
- Mixed case should be used for titles
- The output titles should be designed so that they are arranged consistently through all outputs. For example, content (eg Vital Signs) followed by metric (eg Change from Baseline) e.g. Vital Signs – Change from Baseline.
- Titles should not contain quotation marks or footnote references
- The column headings should be underlined with a row of underscores ('_')
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered
- Column headings containing numbers should be centered
- Column headings should be in sentence case
- In general, the population count should appear in the column header in the form "(N=XXX)"
- "Statistic" should be the column header over n, Mean, SE, n (%) etc.
- As a rule, all columns should have column headings.

TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank
- The left hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned.
- Whole numbers should be right aligned.

- Text values should be left aligned.
- The first letter of a text entry should be capitalized
- Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
- The study drug should appear first in tables with treatments as columns
- In general, only present totals (across treatment groups) at baseline/randomization, and do not present them post randomization, unless the customer specifically requests it.
- If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
- The width of the entire output should match the linesize

Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Median, Minimum, Maximum)
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
  Minimum and maximum: N
  Mean, median and CV%: N + 1
  SD: N + 2

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

```
77 (100.0%)
50 ( 64.9%)
0 ( 0.0%)
```

- Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% will be

presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.

Eg (<0.1%)
(6.8%)
(>99.9%)

Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).

- Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:

- As a rule confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values of confidence intervals should be separated by a comma.
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
- An example is given below:

```
(-0.12, -0.10)
( 9.54, 12.91)
```

P-values:

- P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:

- Ratios should be reported to one more decimal place than the original data.

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2)

Denominators:

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values

- A "0" should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in an end-of-text table or subject listing.

FIGURE OUTPUT CONVENTIONS

- Figures should be provided in RTF files.
- The image should be clear and of high quality when viewed in the Word document, and when printed.
- In general, boxes around the figures should be used.

FOOTNOTE INFORMATION

Footers should be defined as follows:

- A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page
- Table footnotes should appear directly after the body of the table
- The program path and name and version number (if applicable) should appear as footnote 1 at the bottom of the page
- The date/time stamp should appear as footnote 2 at the bottom of the page
- Footnotes should be left-aligned.
- Footnotes should be in sentence case.
- Only "typewriter" symbols are permitted – eg "*", "$", "#", "@", "&" and "+".
- The choice of footnote symbols should be consistent. E.g. if you have the footnote "# indicates last observation carried forward" for one table, the same symbol and footnote should indicate LOCF for all tables.

- If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.
- The page identification in the format Page X of Y (where Y is the total number of pages for the output) should appear in the first footnote, right aligned

Ordering of footnotes should be as follows:

1.) Source data listing reference, if necessary
2.) Abbreviations and definitions
3.) Formulae
4.) P-value significance footnote
5.) Symbols
6.) Specific notes

- Common notes from table to table should appear in the same order.
- The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

PROGRAMMING INSTRUCTIONS

Programming instructions must appear at the end of each table or listing shell. Programming instructions, where necessary, should begin with the words "Programming Note" followed by a colon. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.

EXAMPLE

Customer Name - Protocol Number

Table 14.1.1.1
Subject Disposition

	Number (%) of Subjects		
	Treatment		
Disposition	A (N=XX)	B (N=XX)	Total (N=XX)
Randomised	XX	XX	XX
Completed	XX (XXX.X%)	XX (XXX.X%)	XX (XXX.X%)
Discontinued	XX (XXX.X%)	XX (XXX.X%)	XX (XXX.X%)
Reasons for Discontinuation:			
XXXXXXXXXXXXX	XX (XXX.X%)	XX (XXX.X%)	XX (XXX.X%)
XXXXXXXXXXXX	XX (XXX.X%)	XX (XXX.X%)	XX (XXX.X%)

SOURCE: Listing 16.2.1.1 Page 1 of 1
Abbreviations / definitions
Formulae
P-values...
Symbols...
NOTE 1: Treatment A=XXXXXXXXXXXXXXXXX.
B=XXXXXXXXXXXXXXXXX.
NOTE 2: ...

X:\CUSTOMER\COMPOUND\STUDY\BIOSTATISTICS\PRODUCTION\TABLES\T14_1_1_1.SAS
DDMMMYYYY HH:MM

1.

DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYYY:hh:mm.

SPELLING FORMAT

English UK.

PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening (Visit 1)	Screening
Baseline[a]	Baseline
Day 1 (Visit 2)	Day 1

Long Name (default)	Short Name
Day 2 (Visit 3)	Day 2
Day 3 (Visit 4) * Day 3-5 will be presented under Day 3 (Visit 4)	Day 3
Day 5 (Visit 5)	Day 5
Day 7 (Visit 6) * Day 6-8 will be presented under Day 7 (Visit 6)	Day 7
Day 10 (Visit 7) * Day 9-11 will be presented under Day 10	Day 10
Day 14 (Visit 8)	Day 14
Day 17-18 (Visit 9)	Day 17-18
Day 21 (Visit 10)	Day 21
Day 24-25 (Visit 11)	Day 24-25
Day 28 (Visit 12)	Day 28
Day 35 (Visit 12a)	Day 35
Day 42 (Visit 13)	Day 42
Day 49 (Visit 13a)	Day 49
Day 56 (Visit 14)	Day 56
Day 70 (Visit 15)	Day 70
Day 84 (Visit 16)	Day 84
CRF End of Treatment (Visit 17)	CRF EOT

Long Name (default)	Short Name
Derived End of Treatment[b]	DER EOT
Follow-up 4 Weeks after End of Treatment (Visit 18)	FU 4 WKS EOT
Unscheduled Visit XX.XX[c]	UNSCH XX.XX
Start of Extended Treatment[d]	ST EXT TRT
Extended Treatment Visit XX[d]	EXT TRT VXX
End of Extended Treatment[d]	END EXT TRT
Follow-up 4 Weeks after End of Extended Treatment[d]	FU 4WKS END EXT TRT
[a]A Baseline visit will be programmatically added to outputs (where applicable) based on the derived baseline flag. [b]Derived End of Treatment visits will be programmatically added to outputs where applicable. [c]In chronological order in between scheduled visits, as applicable. [d]Extended Treatment visit will not be included in outputs but will form part of ADaM datasets.	

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Baseline DRC-adjudicated disease category,
- Patient number,
- Date (where applicable).
- Prior Antifungal Therapyat Time of Enrollment to Olorofim

"Nature of response to prior antifungal therapy at time of enrollment to olorofim trial" in eCRF page "Pre-Study Course for Fungal Infection Under Study".

CRF Page: Nature of response to prior antifungal therapy at time of enrollment to Olorofim trial?	(To be presented as) Subgroup "**Prior antifungal therapy response**", categories:

Refractory / Failing →	"Active (Uncontrolled)"
Stable / Persistent →	"Active (Stable)"
Patients with no response entered (missing) or where response is "Unable to judge" (since detail of unable to judge showed all patients had no therapy or too brief) →	"No therapy/too brief"
Partial →	"Improved"
Complete →	"Improved"
Multiple →	"Multiple"
Note: If we expect multiple responses per patient, use the worst outcome (i.e. worst=refractory/failing,then stable/persistent, unable to judge, partial, complete)	

- Immuno suppression status
- Programming note; summary of primary disease type shown below. Medical review and final subgroup categories confirmed in spreadsheet "Immunosuppression_F2G_[redacted]

UDPTCoded	Coded
AIDS	ModIS
CF	ModIS
CGD	ModIS
GenMedical	LowIS
HemeMalig	HIghIS
HSCT	HIghIS
ImmuneDefect	ModIS
LungTx	ModIS
None	LowIS
NonHemeMalig	ModIS
OtherSOT	ModIS

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT-EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known/Partial/ Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known/Partial/ Missing	Not TEAE
Partial, could be on or after study med start date OR Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR, CONCOMITANT AND ANTIFUNGAL MEDICATIONS, AND NON-MEDICATION PROCEDURES:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If study med start date <= stop date <= end of treatment and start date < study med start date assign as both prior and concomitant If study med start date <= start date <= end of treatment assign as concomitant If start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If study med start date <= stop date <= end of treatment and start date < study med start date assign as both prior and concomitant If study med start date <= start date <= end of treatment assign as concomitant If start date > end of treatment, assign as post treatment
	Missing	If start date < study med start date assign as both prior and concomitant If study med start date <= start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If study med start date <= stop date <= end of treatment and start date < study med start date assign as both prior and concomitant If study med start date <= start date <= end of treatment assign as concomitant If start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If study med start date <= stop date <= end of treatment and start date < study med start date assign as both prior and concomitant If study med start date <= start date <= end of treatment assign as concomitant If start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If start date < study med start date assign as both prior and concomitant If study med start date <= start date <= end of treatment assign as concomitant If start date > end of treatment, assign as post treatment

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, assign as prior If study med start date <= stop date <= end of treatment assign as both prior and concomitant If stop date > end of treatment, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If study med start date <=stop date <= end of treatment assign as both prior and concomitant If stop date > end of treatment, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 3. EQ-5D-5L HIS CALCULATION

Table 2. Parameter estimates for main-effects models.

Dimension/level	Model 1: cTTO (Tobit with heteroscedasticity, censored at −1, RE) (preferred model)		
	Estimate	SE	*P* value
MO2	−0.096	0.015	<.0001
MO3	−0.122	0.016	<.0001
MO4	−0.237	0.018	<.0001
MO5	−0.322	0.016	<.0001
SC2	−0.089	0.014	<.0001
SC3	−0.107	0.017	<.0001
SC4	−0.220	0.018	<.0001
SC5	−0.261	0.016	<.0001
UA2	−0.068	0.015	<.0001
UA3	−0.101	0.016	<.0001
UA4	−0.255	0.013	<.0001
UA5	−0.255	0.013	<.0001
PD2	−0.060	0.013	<.0001
PD3	−0.098	0.017	<.0001
PD4	−0.318	0.015	<.0001
PD5	−0.414	0.017	<.0001
AD2	−0.057	0.014	<.0001
AD3	−0.123	0.018	<.0001
AD4	−0.299	0.016	<.0001
AD5	−0.321	0.015	<.0001