

## **PROTOCOL A8851008**

# **A PROSPECTIVE, OPEN-LABEL STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY & EFFICACY OF ANIDULAFUNGIN WHEN USED TO TREAT CHILDREN WITH INVASIVE CANDIDIASIS, INCLUDING CANDIDAEMIA**

## **Statistical Analysis Plan (SAP)**

Version: 6

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Date: 05 October 2016

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## 1. AMENDMENTS FROM PREVIOUS VERSION(S)

This SAP is an amendment of version 1.0.

The analysis of the global response endpoint has been clarified. Other minor changes have been made to bring the SAP in agreement with Protocol Amendment 3.

This SAP is an amendment of version 2.0. The changes have been made to bring the SAP in agreement with protocol Amendment 4. The primary changes for Protocol Amendment 4 allow enrolment of subjects with *Candida* endocarditis and *Candida* osteomyelitis.

This SAP is an amendment of version 3.0. The changes have been made to tighten up the definition of the global response endpoint.

This SAP is an amendment of version 4.0. The changes have been made to conduct additional analysis with subjects who completed study treatment.

This SAP is an amendment of version 5.0. This amendment reflects the changes that were made in protocol amendments 8 and 9, which include expansion of enrolment criteria to include infants (aged 1 month - < 2 years) who do not have microbiologically confirmed *Candida* but who are at high risk of candidiasis, analysis of pharmacokinetic parameters of polysorbate 80, and addition of an interim analysis.

## 2. INTRODUCTION

Anidulafungin is a member of the echinocandin class of antifungals and exhibits fungicidal activity against *Candida* species. In the United States, anidulafungin is approved for the treatment of candidaemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis). In Canada and Europe, anidulafungin carries a similar indication and is approved for the treatment of invasive candidiasis/candidemia in adult non-neutropenic patients. To date, there are no clinical studies evaluating anidulafungin in paediatric subjects with invasive *Candida* infection. This study will assess the pharmacokinetics, safety and efficacy of anidulafungin in subjects 1 month to <18 years of age with invasive candidiasis, including candidemia (ICC). Exposure-response relationships of anidulafungin and polysorbate 80 will also be assessed in a population pharmacokinetic-pharmacodynamic (PK-PD) analysis.

### 2.1. Study Design

This prospective, open-label, non-comparative study will assess the safety and efficacy of anidulafungin when used to treat children between the ages of 1 month and <18 years with invasive candidiasis, including candidemia (ICC).

To participate in this study, at the time of enrolment subjects must have either a confirmed diagnosis of ICC (based on the growth of *Candida* sp. from a culture obtained from a normally sterile site within 96 hours prior to enrollment), or mycological evidence highly suggestive of *Candida* sp. (eg, the growth of yeast in culture and/or the direct microscopic visualization of yeast, hyphae or pseudohyphae from a sample obtained from a normally sterile site within 96 hours prior to enrolment). Subjects may enroll and initiate study

treatment prior to culture confirmation of *Candida* sp. If culture confirmation is not obtained, subjects may remain in the study and receive study treatment at the discretion of the investigator. Should the investigator choose to withdraw the subject from study treatment, the subject will be required to return for the 2-week and 6-week follow-up visits.

In order to accelerate the availability of PK and safety data in the lowest age group (1 month to < 2 years), the study population is broadened only in this age group to include children at risk for invasive candidiasis. Thus, eligibility criteria have been modified in Amendment 9 to additionally allow enrollment of infants (aged 1 month - < 2 years) who do not have microbiologically confirmed *Candida* but who are at high risk of candidiasis, and for whom the investigator considers antifungal therapy with at least 5 days of IV anidulafungin to be appropriate.

All subjects meeting screening criteria will receive IV anidulafungin. On Day 1, subject is to receive a loading dose of 3.0 mg/kg (not to exceed 200 mg). Subject is then to receive a daily maintenance dose of 1.5 mg/kg (not to exceed 100 mg) from Day 2 onwards. Subjects will receive treatment (either solely anidulafungin, or anidulafungin followed by oral fluconazole) for a minimum duration of 14 days from the time of the last negative culture (defined as the second of two consecutive negative cultures, separated by at least 24 hours, following the last positive culture) and improvement of clinical signs and symptom of candidemia or invasive candidiasis.

Subjects without microbiologically confirmed *Candida* infection will be treated with IV anidulafungin at the discretion of the investigator to a maximum of 35 days. Subjects may be switched to oral fluconazole (6-12 mg/kg/day, maximum 800 mg/day) after at least 5 days of IV anidulafungin treatment.

In subjects with *Candida* endocarditis and *Candida* osteomyelitis who require continued treatment beyond the maximum total treatment duration (49 days), this treatment will be considered outside the context of this clinical trial and study drug will not be supplied by the Sponsor. For the purpose of study treatment evaluation, Day 35 (for subjects who require continued IV treatment) or Day 49 (for subjects who required continued oral therapy) will be considered the last day of study drug treatment. These subjects are also required to return for the 2-week and 6-week follow-up visit following the last dose of study drug.

At selected investigator sites, anidulafungin pharmacokinetics will be assessed in the first 6 subjects between 1 month to <2 years of age to confirm whether or not the recommended dosing regimen contained within the protocol for this age group is appropriate.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success, failure or indeterminate at the EOIVT, EOT, 2-week FU and 6-week FU visits. Rates of relapse (recurrence) and/or new infection will be assessed at the FU visits. Safety will be evaluated through assessment of adverse events and monitoring of clinical laboratory tests (hematology and serum chemistry), temperature, and physical examination results. All subjects will be followed for safety through the 6-week FU visit.

### 2.1.1. Study Drug and Dosing

This is a one arm study. All subjects meeting screening criteria will receive IV anidulafungin. On Day 1, subject is to receive a loading dose of 3.0 mg/kg (not to exceed 200 mg). Subject is then to receive a daily maintenance dose of 1.5 mg/kg (not to exceed 100 mg) from Day 2 onwards. Subjects will be stratified by age (1 month - <2 years, 2 - <5 years, and 5 - <18 years). Subjects may be switched to oral fluconazole (6-12 mg/kg/day, maximum 800 mg/day) after at least 5 days of IV treatment, provided that the pre-specified criteria are met.

### 2.1.2. Sample Size

The planned enrolment is approximately 60 evaluable subjects (those subjects who have received at least one dose of anidulafungin and have confirmed *Candida* infection).

## 2.2. Study Objectives

### Primary Objective

Objective 1: *To assess the safety and tolerability of anidulafungin when used to treat children with invasive candidiasis, including candidemia.*

This assessment will be based on the reports of adverse events throughout the study, laboratory tests, and physical examination results.

### Secondary Objectives

Objective 1: *To assess the efficacy of anidulafungin, as measured by global response, at the following time points: EOIVT, end of treatment (EOT), 2-week follow-up (FU) visit and 6-week FU visit.*

This assessment will be based on assessment of the clinical and microbiological responses categorized as one of the possible outcomes: success, failure, or indeterminate. The objective will be accomplished by presenting frequencies and percentages of global success for each time point overall and by age category (1 month - <2 years, 2 - <5 years, and 5 - <18 years).

Objective 2: *To explore pharmacokinetic parameters of anidulafungin in children aged 1 month to <2 years following IV infusion of anidulafungin (AUC<sub>24</sub> and C<sub>max</sub>).*

This pharmacokinetic objective will be addressed in a separate analysis plan.

Objective 3: *To explore pharmacokinetic parameters of polysorbate 80 following IV infusion of anidulafungin (area under curve over dosing interval (AUC<sub>24</sub>) and peak concentration (C<sub>max</sub>).*

This pharmacokinetic/pharmacodynamic (PK-PD) objective will be addressed in a separate analysis plan.

Objective 4: *To explore the exposure-response (safety and efficacy endpoints) relationship of anidulafungin using a nonlinear mixed effects approach as appropriate, including exploring the association between PK-PD index (eg, AUC/MIC) and efficacy endpoints.*

This pharmacokinetic/pharmacodynamic (PK-PD) objective will be addressed in a separate analysis plan.

Objective 5: *To assess rates of relapse (recurrence) at the Week 2 and Week 6 FU visits.*

The objective will be accomplished by presenting the frequencies and percentages of relapse (recurrence) for each follow up visit overall and by age category (1 month - <2 years, 2 - <5 years, and 5 - <18 years).

Objective 6: *To assess rates of new infection at the Week 2 and Week 6 FU visits.*

The objective will be accomplished by presenting the frequencies and percentages of emerging infection for each follow up visit overall and by age category (1 month - <2 years, 2 - <5 years, and 5 - <18 years).

Objective 7: *To assess all-cause mortality during study therapy and FU visits.*

The objective will be accomplished by presenting the proportion of deaths due to all causes for each time point overall and by age category (1 month - <2 years, 2 - <5 years, and 5 - <18 years) at EOIVT, EOT and 2 week and 6 week follow-up visits. The mortality rates will also be described using the Kaplan-Meier methods of summarizing survival.

### **3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING**

#### **3.1. Interim Analyses**

Subjects will be stratified by age (1 month - <2 years, 2 - <5 years, and 5 - <18 years), allowing  $20 \pm 2$  in each stratum. An interim analysis to assess safety, PK and efficacy will be performed after approximately  $20 \pm 2$  for age cohorts 2 to <5 years and 5 to < 18 years groups have completed the study.

The details of the dissemination plan (Tables, Listings and Figures) for subpopulation (age cohorts 2 to <5 years and 5 to <18 years) documented in [Appendix 2](#).

#### **3.2. Final Analysis**

Final analysis will be conducted after the database is released.

### **4. HYPOTHESES AND DECISION RULES**

#### **4.1. Statistical Hypotheses**

As this is a descriptive study, no hypothesis testing will be performed.

## 4.2. Statistical Decision Rules

All analyses will be considered descriptive; therefore, no statistical tests of hypotheses will be performed.

## 5. ANALYSIS SETS

The main subject populations to be used for the analysis are a Modified-Intent-to-Treat (MITT) population and a safety population.

The MITT population will be the primary efficacy analysis population. The PP population will be used in additional supportive analyses of efficacy. The safety population will be used in all analyses of safety. There will be an additional PK population.

### 5.1. Modified Intent-To-Treat Analysis Set

The Modified Intent-To-Treat (MITT) population is defined to be the set of all subjects who have received at least one dose of study drug and who have a confirmed *Candida* infection. This means that the subject must have a positive culture for *Candida* sp from cultures obtained within 96 hours before study entry or at screening.

Note: Due to logistical issues at the local level and the timing of screening activities/treatment initiation, subjects whose qualifying culture for study entry was collected just outside the 96 hour window (ie, within 5 days) will be included in the MITT population.

### 5.2. Safety Analysis Set

This set consists of randomized subjects receive at least one dose of study medication. Subjects will be analyzed according to treatment received, ie, as treated.

### 5.3. Other Analysis Sets

#### 5.3.1. Per-Protocol Analysis Set

The Per-Protocol (PP) analysis set will consist of the subjects in the MITT population, who in addition:

- Have completed a minimum of 10 days of treatment with IV anidulafungin, unless declared a clinical and/or microbiologic failure;
- Have received total antifungal treatment (IV only, IV+Oral) for a minimum duration of 14 days, unless declared a clinical and/or microbiologic failure;
- Have not received more than 48 hours of systemic antifungal therapy (for treatment of current *Candida* infection) prior to first dose of study drug;
- Must not have a prosthetic device and/or vascular catheter (including central venous catheter or an implantable port) at a suspected site of infection are to be excluded, unless the device is removed at study entry or soon after first dose of study drug;

- Have not taken more than 1 day of protocol prohibited antifungal therapy concomitant with study therapy, unless declared a clinical and or microbiologic failure;
- Have reached the 6 weeks Follow up visit unless the subject died or withdrew consent prior to 6 week follow up;

And also exclude those subjects with protocol violations that could have an impact on the efficacy endpoints (See [Section 5.3.2](#)).

### **5.3.2. Pk Analysis Set**

The first 6 subjects aged between 1 month to <2 years will constitute the PK sub-study population. Their data will be combined with all other subjects' safety data for the analyses using the safety population. In addition, demography, medical history, adverse events and efficacy (in those subjects who received anidulafungin as monotherapy for treatment purposes) will be summarized for these 6 subjects alone, and patient profiles will be generated for each of these subjects to allow examination of all their data. They will be presented as a separate group within the listings.

### **5.3.3. Safety ANALYSIS SET**

This set consists of all subjects who have received at least one dose of study medication.

### **5.4. Treatment Misallocations**

Not Applicable.

### **5.5. Protocol Deviations**

The following sections describe any protocol deviations that relate to the statistical analyses.

It is possible that unexpected deviations will arise, becoming known only after the study has been active for a long period of time; hence more deviations may be added. A full list of protocol deviations for the study report will be compiled prior to database closure. As of this writing, the protocol deviations can all be found in [Section 5.5.1](#) and [Section 5.5.2](#) below.

Only protocol deviations that are thought to affect the primary efficacy endpoint will be considered.

#### **5.5.1. Deviations Assessed Prior To Treatment Administration**

At screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 4.1 and 4.2 of the protocol. Granted exceptions to the inclusion or exclusion criteria are not expected to occur. Any subject who enters the study when the inclusion or exclusion criteria would have prevented entry will be considered to have had a protocol deviation.

### 5.5.2. Deviations Assessed Post-Treatment Administration

Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

- If switched to fluconazole, and not all switching criteria, as listed in Section 5.1 of the protocol were met;
- Receipt of any excluded concomitant medications;
- Receipt of the incorrect dose, not including allowed dose escalations and reductions;
- Incorrect administration of treatment;
- Incorrect duration of treatment;
- Non-compliance to study medication, which means a subject should have taken at least 80% of his/her planned doses.

## 6. ENDPOINTS AND COVARIATES

This section defines endpoints and covariates only. Statistical analysis details are found in [Section 8](#).

### 6.1. Efficacy Endpoint(s)

The efficacy endpoints are all secondary endpoints.

#### 6.1.1. Global Response at the End of IV Treatment (EOIVT)

##### 6.1.1.1. Global Response Determination at EOIVT

Global response at EOIVT is based on assessment of clinical and microbiological response provided by the investigator at this time point, and will be programmatically determined as follows:

**Success:** A patient will be categorized as having successful response if there is a clinical response of cure or improvement and microbiological eradication or presumed eradication.

**Failure:** A patient will be categorized as having an unsuccessful response if there is a clinical response of failure and/or unsuccessful microbiological response (persistence or new infection at FU or relapse at FU).

**Indeterminate:** A patient will be categorized as indeterminate if there is a clinical response of indeterminate and /or microbiological response of indeterminate and neither clinical response is a failure nor unsuccessful microbiological response (persistence or new infection or relapse).

A global response determination of failure at EOIVT will be carried forward programmatically to all subsequent visits.

### 6.1.1.2. Investigator Determination of Clinical and Microbiologic Response at EOIVT

As described in [Section 6.1.1.1](#), global response will be derived programmatically based on the investigator's assessment of clinical and microbiologic response.

Definitions of clinical and microbiologic response, which investigators are asked to follow, are listed below:

#### **Clinical Response**

**Cure:** Resolution of sign and symptoms attributed to *Candida* infection; no additional systemic or oral antifungal treatment required to complete the course of therapy.

**Improvement:** Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic or oral antifungal treatment required to complete the course of therapy.

#### ***Important Notes:***

- Initiating or resuming oral antifungal therapy following EOT for prophylactic purposes is permitted, and does not reflect a requirement for additional systemic antifungal therapy for treatment purposes, and therefore does not constitute treatment failure. (Note: It must be clear in the project database that administration of additional antifungal therapy is for prophylactic purposes, otherwise it will be deemed as being administered for treatment of continued infection, in which case study drug treatment will be considered clinical failure.)
- Administration of non-absorbable antifungal agent is not considered systemic antifungal treatment in the context of this study.

**Failure:** No significant improvement in signs and symptoms, or death due to the *Candida* infection. Subjects must have received at least 3 doses of study medication to be classified as a failure.

**Indeterminate:** Evaluation cannot be made due to withdrawal from the study prior to assessment of cure or failure. Subjects who receive fewer than 3 doses of study medication will be assigned as a clinical efficacy response of indeterminate.

#### **Microbiological Response**

**Eradication or presumed eradication:** Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful clinical outcome.

**Persistence (documented or presumed):** Any baseline *Candida* sp. is present in repeat cultures, or culture data are not available for subject with a clinical outcome of failure.

**Indeterminate:** Culture data are not available for a subject with a clinical outcome of indeterminate.

### 6.1.2. Global Response at the End of all Treatment (EOT)

Global response at EOT will be programmatically determined utilizing the same global response, clinical response and microbiologic response definitions for EOIVT, described in [Section 6.1.1.1](#) and [Section 6.1.1.2](#).

A global response determination of failure at EOT will be carried forward programmatically to all subsequent visits.

### 6.1.3. Global Response at the 2 and 6 Week Follow-Up Visits

Global response at the 2 and 6 Week Follow-up Visits will be programmatically determined utilizing the same global response definition described in [Section 6.1.1.1](#).

Clinical and microbiologic definitions to be used for programmatic global response determination at the 2 and 6 Week Follow-Up Visits are as follows:

#### **Clinical Response**

**Cure:** Resolution of sign and symptoms attributed to *Candida* infection; no additional systemic or oral antifungal treatment required to complete the course of therapy.

**Improvement:** Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic or oral antifungal treatment required to complete the course of therapy.

#### ***Important Notes:***

- Initiating or resuming oral antifungal therapy following EOT for prophylactic purposes is permitted, and does not reflect a requirement for additional systemic antifungal therapy for treatment purposes, and therefore does not constitute treatment failure. (Note: It must be clear in the project database that administration of additional antifungal therapy is for prophylactic purposes, otherwise it will be deemed as being administered for treatment of continued infection, in which case study drug treatment will be considered clinical failure). Thus, use of oral prophylactic antifungal therapy following EOT does not constitute treatment failure.
- Administration of non-absorbable antifungal agent is not considered systemic antifungal treatment in the context of this study.

**Failure:** No significant improvement in signs and symptoms, or death due to the *Candida* infection. Subjects must have received at least 3 doses of study medication to be classified as a failure.

**Indeterminate:** Evaluation cannot be made to withdrawal from the study prior to assessment of cure or failure. Subjects who receive fewer than 3 doses of study medication will be assigned as a clinical efficacy response of indeterminate.

### **Microbiological Response**

**Eradication or presumed eradication:** Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful clinical outcome.

**Persistence (documented or presumed):** Any baseline *Candida* sp. is present in repeat cultures, or culture data are not available for subject with a clinical outcome of failure.

**Indeterminate:** Culture data are not available for a subject with a clinical outcome of indeterminate.

**Relapse (recurrence):** Any baseline *Candida* sp. isolated following eradication (documented or presumed); or culture data are not available for a subject with a clinical response of failure after a previous response of success; prophylactic treatment with oral antifungal agents is not sufficient to document a relapse.

**New Infection:** Subject presenting with clinical failure with the emergence of new *Candida* sp. at the original site of infection or at a distant site of infection;

A global response determination of failure at the 2 Week Follow Up will be carried forward programmatically to all subsequent visits.

#### **6.1.4. Concomitant Antifungal Therapy**

Global response at EOIVT, EOT, 2 and 6 Week Follow up will be set to failure following the use of a concomitant medication with activity for any baseline *Candida* spp., based on the following algorithm for handling the global response,

- If a subject takes two or more days of antifungal medications (as identified by the clinical team) after the start of study medication until the end of treatment for any reason, they are imputed to failure for all visits that occur after the antifungal medication was taken.
- If a subject takes one day of antifungal medication after the start of study medication until the end of treatment for the reason “lack of efficacy” they are similarly imputed to failure for all visits that occur after the antifungal medication was taken. The clinical team will determine whether the antifungal medication has been used for “lack of efficacy”.

- In the FU period, if a subject takes at least one day of antifungal medication for reason of “lack of efficacy”, they are imputed to failure for all visits that occur after the antifungal medication was taken. Again, the clinical team will determine whether the antifungal medication has been used for “lack of efficacy”.

### **6.1.5. Rate of Response Based on Clinical Cure and Microbiological Success at EOIVT, EOT, 2 and 6 Week Follow-Up Visits**

The rate of response will be reported as a subset of subjects who have a global response of success which will be defined as subject with clinical cure and microbiologic eradication or presumed eradication.

#### **6.1.5.1. Rate of Relapse at the 2 and 6 Week Follow-Up Visits**

The rate of relapse, defined as a microbiologic response of relapse, at the 2 and 6 Week Follow-Up Visit will be reported.

#### **6.1.5.2. Rate of New Infection at the 2 and 6 Week Follow-Up Visits**

The rate of new infection, defined as a microbiologic response of new infection, at the 2 and 6 Week Follow-Up Visit will be reported.

#### **6.1.5.3. All-Cause Mortality During Study Therapy and Follow-Up Visits**

The mortality rate at EOIVT, EOT, 2 week and 6 week follow-up will be calculated as the proportion of subjects who died by these timepoints in the trial, based on the number of subjects in the study population at the start of the trial.

#### **6.1.5.4. Time to Death**

For this analysis, time to death will be measured from the first dose of study medication in days. For subjects who died, time to death is defined as:

$$T = \text{date of death} - \text{first treatment date} + 1$$

where date of death will be recorded on the End of Study page and/or Infection Notice of Death page. These observations will be regarded as events for the purposes of time to event analyses.

Subjects who are not known to have died, will be censored at their last known survival date taken as the latest date in the database. Time to death is defined as:

$$T = \text{latest date in the database} - \text{first treatment date} + 1$$

where the latest date is expected to be the date of the End of Study visit.

## **6.2. Safety Endpoints**

The safety assessment is the primary endpoint of the study. The following safety assessments will be performed:

### **6.2.1. Adverse events**

Any events occurring following start of treatment or increasing in severity will be counted as treatment emergent.

For the standard required analysis, events that occur in a non-treatment period (up to 30 days after last dose of study drug) will be counted as treatment emergent and attributed to the previous treatment taken.

### **6.2.2. Laboratory Tests**

Hematology and blood chemistry will be performed by the local laboratory at all visits according to the protocol.

To determine if there are any clinically significant laboratory abnormalities, the hematological and clinical biochemistry safety tests will be assessed against the criteria specified in the sponsor reporting standards. The assessment will take into account whether each subject's baseline test result is within or outside the laboratory reference range for the particular laboratory parameter.

### **6.2.3. Physical Examination and vital signs**

- A complete physical examination (including vital signs) at Screening;
- A targeted physical examination on Days 3, 7, 10, 11-34 (every 3 days), EOIVT, EOT, Week 2 FU visit, and Week 6 FU visit.

The number of subjects whose physical examination significantly changed from the previous physical examination will be assessed for each visit.

- Vital signs (including temperature) at Screening, daily through EOT, Week 2 FU visit, and Week 6 FU visit.

### **6.2.4. Fundoscopic Examination**

The fundoscopic examination assessment results are reported as normal/abnormal or present/absent at Screening for each eye and at EOIVT, EOT, Week 2 FU visit, and Week 6 FU visit if the Screening fundoscopic examination is positive for endophthalmitis. The Screening visit data will be summarized for all subjects.

## **6.3. OTHER Endpoints**

There are no other endpoints planned for this study.

## **6.4. Covariates**

As this is a descriptive study, there are no covariates needed for this study.

As an objective of the study is to examine safety and efficacy within the different age groups, a number of the variables will be presented split into the age categories: 1 month - <2 years, 2 years - <5 years and 5 - <18 years.

Global response rates for each of the different *Candida* species will also be reported.

Site of infection is of interest to see whether there are different response rates dependent on the site of infection. Global response rates will be presented for each of the three categorizations for rate of response:

- i. Blood only;
- ii. Blood and other sterile site;
- iii. Sterile site (other than blood) only.

Dependent on numbers of subjects, global response may also be presented by different underlying diseases.

- neutropenic status (<500 neutrophils vs  $\geq$ 500 neutrophils.)
- allogeneic BMT vs not allogeneic BMT

## 7. HANDLING OF MISSING VALUES

For global response, missing values are treated as failures. Sensitivity analyses will also be performed in which subjects with missing values for global response are excluded from the analysis.

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

## 8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

### 8.1. Statistical METHODS

#### 8.1.1. Analyses for Binary Data

Response rates and mortality rates at each timepoint will be presented with exact 95% confidence intervals for binomial proportion, using the Clopper-Pearson method which employs the F-distribution to obtain percentiles of the binomial distribution (Collett 1991).<sup>3</sup>

#### 8.1.2. Analyses for Time-to-Death Data

The analysis of time-to-death will be summarized graphically using the Kaplan-Meier product limit estimator.

Subjects who do not have the event of interest will be censored at the last available observation, as defined in [Section 6.1.5.4](#). A censoring variable will be used, with a value of 1 denoting that the subject had the event of interest and 0 indicating that the subject is censored. A time variable is also required, defined as  $T = [\max(\text{date of event, latest date in database}) - \text{first treatment date} + 1]$ . Summaries of observed median survival time with upper and lower quartiles will be provided.

## 8.2. Statistical Analyses

Efficacy analyses will be performed on the MITT population for all analyses, with additional supportive analyses being performed using the PP populations where stated. Visit windows will be used (see [Appendix 1.1](#)). The observation occurring closest to the planned visit day (non-missing) will be summarized. In the instance that 2 observations are equidistant, the latest observation will be used.

### 8.2.1. Primary Analysis

The primary analysis is to examine safety and tolerability of anidulafungin. The set of subjects for this evaluation will be the Safety population. The following parameters will be summarized: rates of discontinuation, adverse events, visual tests, physical examination, ECG findings (if applicable), and laboratory abnormalities. The analysis methods are described in [Section 8.2.4](#).

### 8.2.2. Secondary Analyses

#### Global Response

For each age category, analysis of global response rate at EOIVT, EOT, 2 weeks FU, and 6 weeks FU will be produced for the MITT analysis set. The summary will include the number of observations and estimated rates overall and for each age category.

This analysis will also be performed for each *Candida* species, combining across the age groups.

In order to investigate the robustness of the results, a sensitivity analysis will be carried out. This analysis will investigate the effect of 'indeterminate' and 'missing' global response on the analysis by excluding these subjects from the analysis of global response.

Analysis of global response success rate only for those subjects who completed study treatment at EOIVT, EOT, 2 week follow-up and 6 week follow-up visits will be produced for the MITT population.

A summary of Global Response, Clinical Response and Microbiological response will be produced for the MITT population. For Clinical Response, this will give a count of the number of subjects in each of the categories 'Cure', 'Improvement', 'Failure', 'Indeterminate', and 'Missing'. For Microbiological response, this will give a count of the number of subjects in each of the categories 'Eradication', 'Presumed Eradication', 'Persistence', 'Indeterminate', and 'Missing'. This will be presented overall, for each age category and for each *Candida* species.

#### Rate of Relapse (Recurrence)

For each age category, the number of included patients, number of patients who relapsed, and the percent relapsed will be calculated. The denominator for the rate is the number of subjects in that population at baseline. This analysis will be done in the MITT analysis set for the Week 2 and Week 6 FU visits.

This analysis will also be performed for each *Candida* species, combining across the age groups.

#### Rate of New Infection

For each age category, the number of included patients, number of patients with new infection, and the percent with new infection will be calculated. The denominator for the rate is the number of subjects in that group and analysis set at baseline. This analysis will be done in the MITT analysis set for the Week 2 and Week 6 FU visits.

This analysis will also be performed for each *Candida* species, combining across the age groups.

#### All-cause Mortality

For each age category, all cause mortality during study therapy and FU visits will be performed in the MITT analysis set using the same methods described in [Section 8.1.1](#)

All causes of death will be summarized.

This analysis will also be performed for each *Candida* species, combining across the age groups.

#### Time To Death

Time to death (all-cause) will be analyzed using methods of [Section 8.1.2](#), on the MITT analysis set.

For each age category, the number of patients who died, who were censored during the study, and who were still alive at each FU visit will be summarized by age stratum.

This analysis will also be performed for each *Candida* species, combining across the age groups.

### **8.2.3. Analyses for PK-PD Data**

The analyses in support of the PK-PD objective will be described in a separate document.

### **8.2.4. Safety Analyses**

No formal statistical analyses are planned for safety data. The safety and other endpoints detailed in [Section 6.2](#) will be listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations will consist of subjects from the safety analysis set. Additionally, demography, medical history and adverse events will be presented separately for the MITT population.

**8.2.4.1. Treatment and Disposition of Subjects**

Subject disposition and the number of subjects analyzed for efficacy, and safety (adverse events and laboratory data) will be presented by age category. Frequency counts will be supplied for subject discontinuation(s) by age category.

Data will be reported in accordance with the sponsor reporting standards.

**8.2.4.2. Demographic Data and Medical History**

Frequencies for demographic data will be provided for age, race, height, and weight. Each will be summarized by sex at birth and 'All Subjects' for each age category separately and overall in accordance with the sponsor reporting standards.

The subjects in the PK population analysis set will have an additional table summarizing their demography.

Medical history will be summarized overall and by each age category.

**8.2.4.3. Primary Diagnosis and Site of Infection**

Primary diagnosis will be summarized for each treatment group, and will also be cross tabulated with the site of infection. The sites of infection will be collapsed into 3 categories for summarization purposes:

- i. Blood only;
- ii. Blood and other sterile site;
- iii. Sterile site (other than blood) only.

**8.2.4.4. Discontinuation(s)**

Frequency of subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by age category.

Data will be reported in accordance with the sponsor reporting standards.

**8.2.4.5. Adverse Events**

All adverse events will be coded using the MedDRA dictionary. Frequencies of adverse events will be presented by system organ class, preferred term, age category, and severity level.

All causality treatment emergent adverse events will be presented using two different treatment groupings.

Firstly they will be presented for the one group where all adverse events are counted from start of study to end of follow-up period. This will provide an overall assessment of all adverse events in the study.

Secondly they will be split into time periods within the study:

- Those that occurred from start of study to end of treatment by anidulafungin, including up to end of follow-up period if no other antifungal was administered;
- Those adverse events that started after treatment with another antifungal up until the end of the follow-up period.

This will provide guidance as to which adverse events occurred during treatment with anidulafungin, as opposed to those that occurred during other therapies.

Treatment related treatment emergent adverse events will be presented in two ways:

- Firstly, for those that are considered to be caused by anidulafungin, providing a summary of treatment related adverse events;
- Secondly, for those that are caused by anidulafungin and/or fluconazole, providing a summary of adverse events for the anidulafungin plus fluconazole treatment regimen.

All causality treatment emergent adverse events and treatment related adverse events will also be summarized for the 6 subjects in the PK sub-study analysis set.

Adverse events and serious adverse events will be listed by subject for all age categories.

Adverse events leading to discontinuation or temporary dose reduction will be presented ([Discontinuation\(s\)](#) Section).

Adverse events will be reported in accordance with the sponsor reporting standards.

Additional tables summarizing adverse events that are considered to be potentially indicative of an infusion related reaction which occur during the anidulafungin infusion or within 60 minutes following completion of the anidulafungin infusion will be presented. The adverse event terms of interest are:

Rash, pruritus, chest tightness, vasodilation, flushing, hyperhydrosis, angioneurotic edema, erythema, urticaria, shortness of breath, cough, feeling hot, sweating, diaphoresis, facial swelling plus possible other similar terms to be determined at the end of study. There will be one table for all causality and another for anidulafungin treatment related.

For subjects with infusion reactions or potential infusion related adverse events who also received anesthetic at the same time, the adverse event will be listed along with the anesthetic administered with the relevant start and stop times.

#### **8.2.4.6. Laboratory Data**

Descriptive statistics will be summarized by age category for each baseline measurement as well as for median changes from baseline at each post dose measurement time for laboratory parameters. A listing of laboratory data values and changes from baseline will be provided by age category, subject, test and time.

For each age category, a summary table will present the frequency of subjects with post dose laboratory test abnormalities. All post dose visits will be counted. Listings of values of potential clinical concern will be provided by both subject and by test.

All presentations of laboratory test data will be in accordance with the sponsor reporting standards.

#### **8.2.4.7. Concomitant Medications**

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

#### **8.2.4.8. Treatment Duration**

Duration of treatment will be summarized and split by age category and IV treatment vs. oral treatment as well as total duration. Additionally for subjects whose blood culture became negative during the course of the study, treatment duration will be summarized for the number of days of treatment until the last positive blood culture and the numbers of days of treatment from then until EOT. The number of days of treatment for subjects whose blood cultures remained positive up until EOT will be summarized.

All dosing information will be listed.

#### **8.2.4.9. Physical Examination and Vital Signs**

All physical examination and vital sign data will be provided in the listings.

#### **8.2.4.10. Fundoscopic Examinations**

The fundoscopic examination will be summarized at baseline by age category for each eye for all subjects. The number and percentage of subjects who have normal/abnormal or present/absent results will be presented. For subjects who have subsequent fundoscopic examinations, the numbers of subjects whose fundus has changed, split by whether they results were normal/abnormal or present/absent at Screening, will be presented.

The results of the fundus examination will be listed together for each visit for each subject.

#### **8.2.4.11. Use of Other Anti-Fungal Therapy**

Use of other anti-fungal therapy between EOT and Week 6 FU visit will be tabulated. Use of antifungal therapy within 30 days prior to Screening visit will also be tabulated.

#### **8.2.4.12. Screening and Other Special Purpose Data**

The intravenous catheter details will be listed.

Microbiology and histopathology results will be listed.

Signs and symptoms of ICC will be assessed at Screening, Day 10, EOIVT, EOT, Week 2 FU visit, and Week 6 FU visit and listed.

All Electrocardiogram data will be listed.

Urine or serum pregnancy testing will be performed in all females of child-bearing potential at Screening, EOT (defined as the end of IV anidulafungin if subject is not switched to oral fluconazole, or the end of the oral fluconazole if subject is switched from IV anidulafungin to oral fluconazole) and follow-up visit.

**8.2.5. Summary of Efficacy Analyses**

<b>Endpoint</b>	<b>Analysis Set</b>	<b>Statistical Method</b>	<b>Model/ Covariates/ Strata</b>	<b>Missing Data</b>	<b>Interpretation</b>
Rate of global response at EOIVT	MITT	Descriptive only	Age categories	Failure	Secondary Analysis
Rate of global response at EOIVT	MITT	Descriptive only	Age categories	Missing and indeterminate excluded	Sensitivity
Rate of global response at EOIVT	MITT	Descriptive only	<i>Candida</i> species	Failure	Secondary Analysis
Rate of global response at EOIVT	MITT	Descriptive only	Site of infection	Failure	Secondary Analysis
Rate of global response at EOT	MITT	Descriptive only	Age categories	Failure	Secondary Analysis
Rate of global response at EOT	MITT	Descriptive only	<i>Candida</i> species	Failure	Secondary Analysis
Rate of global response at EOT	MITT	Descriptive only	Site of infection	Failure	Secondary Analysis
Rate of global response at Week 2 FU	MITT	Descriptive only	Age categories	Failure	Secondary Analysis
Rate of global response at Week 2 FU	MITT	Descriptive only	<i>Candida</i> species	Failure	Secondary Analysis
Rate of global response at Week 2 FU	MITT	Descriptive only	Site of infection	Failure	Secondary Analysis
Rate of global response at Week 6 FU	MITT	Descriptive only	Age categories	Failure	Secondary Analysis
Rate of global response at Week 6 FU	MITT	Descriptive only	<i>Candida</i> species	Failure	Secondary Analysis
Rate of global response at Week 2 FU	MITT	Descriptive only	Site of infection	Failure	Secondary Analysis
Rate of relapse at Week 2 FU	MITT	Descriptive only	Age categories	Not Applicable	Secondary Analysis
Rate of relapse at Week 2 FU	MITT	Descriptive only	<i>Candida</i> species	Not Applicable	Secondary Analysis

Rate of relapse at Week 6 FU	MITT	Descriptive only	Age categories	Not Applicable	Secondary Analysis
Rate of relapse at Week 6 FU	MITT	Descriptive only	<i>Candida</i> species	Not Applicable	Secondary Analysis
Rate of new infection at Week 2 FU	MITT	Descriptive only	Age categories	Not Applicable	Secondary Analysis
Rate of new infection at Week 2 FU	MITT	Descriptive only	<i>Candida</i> species	Not Applicable	Secondary Analysis
Rate of new infection at Week 6 FU	MITT	Descriptive only	Age categories	Not Applicable	Secondary Analysis
Rate of new infection at Week 6 FU	MITT	Descriptive only	<i>Candida</i> species	Not Applicable	Secondary Analysis
All-cause mortality rate at EOIVT	MITT	Descriptive only	Age categories	Death	Secondary Analysis
All-cause mortality rate at EOIVT	MITT	Descriptive only	<i>Candida</i> species	Death	Secondary Analysis
All-cause mortality rate at EOT	MITT	Descriptive only	Age categories	Death	Secondary Analysis
All-cause mortality rate at EOT	MITT	Descriptive only	<i>Candida</i> species	Death	Secondary Analysis
All-cause mortality rate at Week 2 FU	MITT	Descriptive only	Age categories	Death	Secondary Analysis
All-cause mortality rate at Week 2 FU	MITT	Descriptive only	<i>Candida</i> species	Death	Secondary Analysis
All-cause mortality rate at Week 6 FU	MITT	Descriptive only	Age categories	Death	Secondary Analysis
All-cause mortality rate at Week 6 FU	MITT	Descriptive only	<i>Candida</i> species	Death	Secondary Analysis
Time to death (all cause mortality)	MITT	Kaplan-Meier	Age categories	Censored	Secondary Analysis

## 9. REFERENCES

1. Pappas, PG et al. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. *Clin Infect Dis* 1999; 29:239-244.
2. Rodríguez-Nunez et al. Incidence and mortality of proven invasive *Candida* infections in paediatric intensive care patients. *Infect Control Hosp Epidemiol* 2001; 22:477-8.
3. Collett, D. (1991), *Modelling Binary Data*, London: Chapman & Hall.

## 10. APPENDICES

### Appendix 1. DATA DERIVATION DETAILS

#### Appendix 1.1. Definition and Use of Visit Windows in Reporting

In order to capture all available data, and allocate each actual (non-missing) assessment to its closest scheduled assessment time, visit windows will be constructed around each scheduled assessment time. The actual assessment time will be calculated based on the subject's date of first dose and the subsequent assessment day. Visit windows will be determined as follows:

If two (or more) scheduled assessments occur in one window, the visit nearest to the scheduled (target) day for the window will be used, with the other(s) excluded from the analysis. If two assessments are equi-distant from the scheduled day (but either side), the assessment performed at the later time should be used. This procedure will be performed separately for each variable.

Day of Assessment	Time Point	Target Day	Definition (Day Window)
Day 1	Screening/Baseline	1	Day 1
Day 3	Day 3	3	Day 2-Day 4
Day 7	Day 7	7	Day 6 – Day 8
Day 10	Day 10	10	Day 9 – Day 11
EOIVT	EOIVT	1-35	EOIVT to EOIVT + 2 days
EOT	EOT	24-49	EOT + 2 days
2 week FU	Week 2 FU	38-63	EOT + 12 days to EOT + 20 days
6 week FU	Week 6 FU	64-77	EOT + 35 days to EOT + 49 days

Screening/Baseline will be defined as the latest evaluation performed prior to the start of therapy.

**Appendix 2. Tables, Listings and Figures for Interim Analysis**

<b>Tables</b>
Subject Evaluation Groups
Discontinuations from study
Discontinuations from Treatment
Demographic Characteristics - Safety Population
Demographic Characteristics - MITT Population
Medical History - Safety Population
Medical History - MITT Population
Anti-infective Stratification (Site of Infection) - MITT Population
Candidemia Risk Factors - MITT Population
Summary of Baseline Candida Species - MITT Population
Anti-infective Stratification Categorization
Analysis of Global Response at EOIVT - MITT Population
Analysis of Global Response at EOIVT - MITT Population (Sensitivity Analysis - Excluding Indeterminate and Missing data)
Analysis of Global Response at EOT - MITT Population
Analysis of Global Response at EOT - MITT Population (Sensitivity Analysis - Excluding Indeterminate and Missing data)
Analysis of Global Response at 2 week follow-up - MITT Population
Analysis of Global Response at 2 week follow-up - MITT Population (Sensitivity Analysis - Excluding Indeterminate and Missing data)
Analysis of Global Response at 6 week follow-up - MITT Population
Analysis of Global Response at 6 week follow-up - MITT Population (Sensitivity Analysis - Excluding Indeterminate and Missing data)
Analysis of Clinical Cure and Microbiologic Success at EOIVT - MITT Population
Analysis of Clinical Cure and Microbiologic Success at EOT - MITT Population
Analysis of Clinical Cure and Microbiologic Success at 2 Week Follow-Up Visit. - MITT Population
Analysis of Clinical Cure and Microbiologic Success at 6 Week Follow-Up Visit. - MITT Population
Summary of Global Response - MITT Population
Summary of Clinical Response - MITT Population
Summary of Microbiological Response - MITT Population
Analysis of Rate of Relapse at 2 week follow-up - MITT Population
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Analysis of Rate of New Infection at 2 week follow-up - MITT Population
Analysis of Rate of New Infection at 6 week follow-up - MITT Population
Summary of Global Response for Site of Infection by Age Group - MITT Population
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Summary of Microbiological Response by Candida species by Age Group- MITT Population
Summary of Global Response According to Neutrophil Status at Baseline (ANC $\leq$ 500 and $>$ 500) - MITT Population
Summary of All Cause Mortality - Safety Population
Summary of All Cause Mortality - MITT Population
Analysis of time to death (All Causality) - Safety population
Analysis of time to death (All Causality) - MITT population
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Temporary Discontinuations or Dose Reductions Due to Adverse Events
Treatment Emergent Adverse Events (All Causalities) - Safety Population
Treatment Emergent Adverse Events by System Organ Class (All Causalities) - Safety Population
Summary of Treatment-Emergent Risk Events (All Causalities) - Safety Population
Treatment Emergent Adverse Events (Treatment Related) - Safety Population
Treatment Emergent Adverse Events by System Organ Class (Treatment Related - Anidulafungin and Fluconazole) – Safety Population
Treatment Emergent Adverse Events by System Organ Class (Treatment Related - Anidulafungin) – Safety Population
Treatment-Emergent Adverse Events by System Organ Class (Treatment Related - Fluconazole) – Safety Population
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Incidence and Severity of Treatment Emergent Adverse Events (Treatment Related) - Safety Population
Incidence and Severity of Treatment Emergent Adverse Events (Treatment Related - Anidulafungin) - Safety Population
Incidence and Severity of Treatment Emergent Adverse Events (Treatment Related - Fluconazole) - Safety Population
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Basic Results Disclosure for Treatment Emergent Serious Adverse Events
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Microbiology Data (Vendor data)
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<b>Figures</b>
Kaplan-Meier Plot of Time to Death - Safety Population
Kaplan-Meier Plot of Time to Death - MITT Population

## Document Approval Record

**Document Name:** A8851008 Statistical Analysis Plan V6 05 October 2016

**Document Title:** A8851008 Statistical Analysis Plan V6 05 October 2016

Signed By:	Date(GMT)	Signing Capacity
PPD	07-Oct-2016 13:51:24	Manager Approval