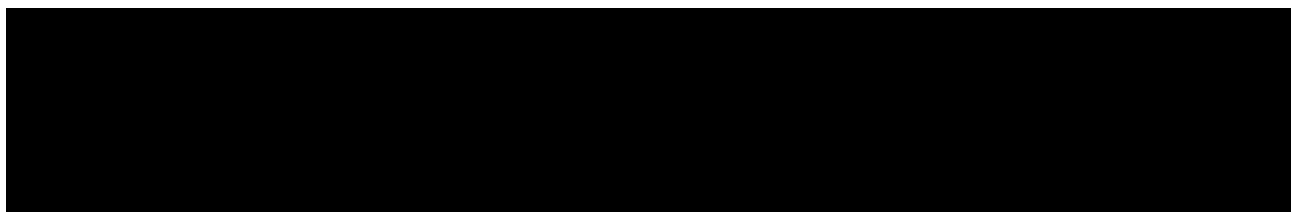




**A Prospective, Open-Label Study To Assess The Pharmacokinetics, Safety & Efficacy
Of Anidulafungin When Used To Treat Children With Invasive Candidiasis, Including
Candidemia**

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Document History

Document	Version Date	Summary of Changes
Amendment 9	16 September 2016	<p>Protocol updated to (1) permit enrollment of subjects at risk for invasive candidiasis in the 1 month - < 2 years age group, including associated updates to schedule of activities, study design, study treatment, study procedures, and microbiological determinations; (2) modify key exclusion criterion, including those related to prior systemic antifungal therapy and removal of prosthetic device and/or vascular catheter at suspected site of infection; (3) add interim analysis; (4) reduce volume of blood required for polysorbate 80 pharmacokinetic samples and add details for preferred sample collection times; (5) provide instructions for withdrawal of subjects without microbiologically confirmed ICC; (6) incorporate minor text revisions to improve clarity of protocol language.</p> <p>See Summary of Changes Document, 16 September 2016</p>
Amendment 8	06 July 2015	<p>Protocol updated to include (1) measurement of polysorbate 80 plasma levels at the request of the Paediatric Committee (PDCO) at the European</p>

		<p>Medicines Agency, including associated updates to secondary objectives and endpoints, schedule of activities, study procedures, pharmacokinetic and statistical sections; (2) removal of plan to extend study to neonates (0 – 1 month of age) since US FDA and PDCO granted a waiver to study anidulafungin in this population; (3) recent Pfizer standard protocol template text, including language regarding (a) lifestyle guidelines; (b) Sponsor's Qualified Medical Personnel; (c) study treatments; (d) adverse event reporting; (e) quality control and quality assurance; (f) ethical conduct of the study; (g) subject informed consent; (h) publication of study results.</p> <p>See Summary of Changes Document, 06 July 2015</p>
Amendment 7	7 January 2013	<p>Protocol updated to include (1) recent Pfizer standard protocol template text, including language regarding females and males of childbearing potential, pregnancy testing and contraception; (2) expected SAEs and additional SAE reporting requirements; (3) medication error reporting requirements.</p> <p>At Korean and Portuguese investigator sites, subjects with <i>Candida</i> endocarditis and <i>Candida</i> osteomyelitis</p>

		are prohibited from participating in the study. See Summary of Changes Document, 07 January 2013
Amendment 6 (Country-specific protocol amendment for Korea)	8 December 2011	At the request of the Korean FDA, sponsor removed all aspects of the protocol related to the enrollment of subjects with <i>Candida</i> endocarditis and <i>Candida</i> osteomyelitis; Korean investigator sites are not permitted to enroll subjects with these conditions.

Amendment 5	23 June 2011	Protocol updated to include section 7.4 Electrocardiogram (ECG) which was inadvertently deleted during the creation of protocol amendment 4 See Summary of Changes Document, 23 June 2011
Amendment 4	19 August 2010	See Appendix 4 Protocol amended to open enrollment up to subjects with <i>Candida</i> endocarditis and <i>Candida</i> osteomyelitis
Amendment 3	21 September 2009	See Appendix 3
Amendment 2	02 July 2008	See Appendix 2
Amendment 1	12 March 2008	See Appendix 1
Original protocol	07 December 2001	N/A

PROTOCOL SUMMARY

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

The primary study objective is to assess the safety and tolerability of anidulafungin when used to treat children with ICC. Additional assessments will include global response at the end of IV therapy (EOIVT) and subsequent time points, exposure-response relationship, the rates of relapse (recurrence) and new infection at follow up (FU) visits, and analysis of time to death during study therapy and follow-up visits.

A sub-study to explore the pharmacokinetic (PK) parameters in children aged 1 month to <2 years will be performed on a limited number of subjects prior to complete enrollment of this age group in this study.

Indication:

Primary therapy of invasive candidiasis, including candidemia, in children between the ages of 1 month and <18 years.

Background and Rationale:

The incidence of systemic invasive fungal infections has risen significantly in the past decade. Infections due to *Candida* spp. account for about 80% of all systemic fungal infections and are the fourth leading cause of all nosocomial bloodstream infections in the United States.¹ The impact of fungal infections on health care and economic expenditures is large and of growing concern. Increases in infection rates are a consequence of growing numbers of at-risk subjects due to advances in transplantation technology and oncology treatment, spread of the Human Immunodeficiency Virus (HIV), use of vascular catheters, and extensive administration of broad-spectrum antibiotics.

In the United States, mortality rates in children with candidemia approach 30%, depending on the specific subject population and clinical setting.^{2,3} Current approved treatments for infections due to *Candida* spp. include polyenes, azoles and echinocandin antifungal agents. Of these, amphotericin B and fluconazole are the most commonly utilized in the paediatric population. Guidelines for use of these agents in the paediatric population have often been extrapolated from adult studies.

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 candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in adults. 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 patients with invasive *Candida* infection. This study will assess the pharmacokinetics, safety and efficacy of anidulafungin in patients 1 month to <18 years of age with ICC.

Exposure-response relationships of anidulafungin will also be assessed in a population pharmacokinetic-pharmacodynamic (PK-PD) analysis.

Anidulafungin is a semi-synthetic lipopeptide synthesized from a fermentation product of *Aspergillus nidulans*. It acts as a non-competitive inhibitor of (1, 3)- β -D-glucan synthase, an enzyme required for synthesis of the cell wall in many pathogenic fungi. Suppression of cell wall glucan synthesis leads to osmotic instability and eventual cell death.

Anidulafungin is active in vitro against a number of important pathogenic organisms, including *Candida* spp., *Aspergillus* spp., and *Pneumocystis jiroveci* (formerly *P. carinii*). It is at least as potent as and often more potent than amphotericin B and fluconazole against *Candida* and *Aspergillus* spp. Activity of anidulafungin against *Candida* spp. is fungicidal and has been demonstrated under a variety of growth conditions.

In animal models, anidulafungin has cleared *Candida* from internal organs and mucosa and led to prolonged survival in lethal infections. Anidulafungin demonstrated efficacy in studies in immunosuppressed and immunocompetent mice systemically infected with *C. albicans* or *C. glabrata* (including fluconazole- and amphotericin B-resistant isolates), immunosuppressed rabbits with fluconazole-resistant esophageal and oropharyngeal candidiasis, and persistently neutropenic rabbits with disseminated *C. albicans* candidiasis.

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 discontinue study treatment but will remain in the study for continued safety monitoring for up to 6 weeks after the last dose of study treatment.

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 be stratified by age (1 month - <2 years, 2 - <5 years, and 5 - <18 years).

Subjects with microbiologically confirmed ICC may be switched to oral fluconazole (6-12 mg/kg/day, maximum 800 mg/day) after at least 10 days of anidulafungin IV treatment, provided that the pre-specified criteria are met. Subjects will receive treatment (either solely IV 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 symptoms 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.

The maximum total treatment duration for all subjects in this study is 49 days, and the maximum allowed treatment duration with anidulafungin is 35 days. The last day of study treatment will be considered the End of Treatment (EOT). It is expected that the majority of subjects will receive study drug in the hospital; subjects will be permitted to complete study medication on an outpatient basis if deemed appropriate by the investigator.

(This paragraph, as well as all text herein related to subjects with Candida endocarditis and Candida osteomyelitis, is not applicable to Korean and Portuguese investigator sites.) 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.

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine or serum pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. If a positive culture is returned, repeat cultures are required at least every 3 days until 2 consecutive cultures separated by 24 hours or more are confirmed to be negative. For subjects without microbiologically confirmed ICC, further cultures will be drawn at the discretion of the investigator.

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. These

subjects may be administered anidulafungin in one of two ways: either as monotherapy or in combination with a second systemic antifungal agent (eg, amphotericin B).

In the event the investigator chooses to administer anidulafungin as monotherapy for the treatment of invasive candidiasis/candidemia, treatment will be administered 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 symptoms of candidemia or invasive candidiasis. In the event the investigator chooses to administer anidulafungin in combination with a second antifungal agent, anidulafungin will be discontinued following the obtainment of required blood samples for pharmacokinetic analysis as specified by the protocol; the data from these subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. After the dosing regimen is confirmed by the Sponsor, enrollment will be opened to additional subjects within this age group at all investigator sites. Subsequent to this time point, the use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted in any subject.

A population PK-PD analysis will also be performed in all other subjects enrolled and will include subjects <2 years of age who are not part of the 6 subject cohort described above, in which 3 to 5 sparse pharmacokinetic samples will be collected.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure 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.

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

Objectives:

Primary

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

Secondary

- To assess the efficacy of anidulafungin, as measured by global response, at the following time points: EOIVT, EOT, 2-week FU visit and 6-week FU visit;
- To explore pharmacokinetic parameters of anidulafungin in children aged 1 month to <2 years following IV infusion of anidulafungin (area under curve over dosing interval (AUC₂₄) and peak concentration (C_{max}));

- To explore pharmacokinetic parameters of polysorbate 80 following IV infusion of anidulafungin (area under curve over dosing interval (AUC_{24}) and peak concentration (C_{max}));
- 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;
- To assess rates of relapse (recurrence) at the Week 2 and Week 6 FU visits;
- To assess rates of new infection at the Week 2 and Week 6 FU visits;
- To assess all-cause mortality during study therapy and FU visits.

Endpoints

Primary Endpoint

- The primary endpoint will be an assessment of the safety and tolerability of anidulafungin.

Secondary Endpoints

- Global response (based on the clinical and microbiological responses) at the EOIVT and subsequent time points;
- Pharmacokinetic parameters of anidulafungin in children aged 1 month to <2 years following IV infusion of anidulafungin: AUC_{24} and C_{max} ;
- Pharmacokinetic parameters of polysorbate 80 following IV infusion of anidulafungin: AUC_{24} and C_{max} ;
- Exposure-response (efficacy and safety endpoints) relationships of anidulafungin using a nonlinear mixed effects approach as appropriate;
- Rates of relapse (recurrence) at the Week 2 and Week 6 FU visits;
- Rates of new infection at the Week 2 and Week 6 FU visits;
- All-cause mortality during study therapy and Follow-Up visits.

Statistical Methods:

The primary analysis will be the evaluation of adverse events throughout the trial, laboratory tests, ECG findings (if applicable), temperature, and physical examination. The set of subjects for this evaluation will be the Safety population, defined as all subjects with at least 1 dose of study medication. The following parameters will be summarized: rates of

discontinuation, adverse events, and laboratory abnormalities. Safety data will be descriptively summarized. Descriptive statistics for categorical data will include frequencies and/or percentages.

Secondary efficacy analyses will be assessed in the Modified Intent-to-Treat (MITT) population, defined as all subjects who have received at least one dose of study drug and who have microbiological confirmation of *Candida* infection. The efficacy analysis will be an assessment of global response, conducted by frequencies and percentages of global response (success, failure).

Other analyses will include rates of relapse (recurrence) and new infection at FU visits, and analysis of time to death during study therapy and FU visits.

Schedule of Activities

	Screening ¹	Daily through EOT	Day 3	Day 7	Day 10	Days 11-34	End of IV Therapy	End of Oral Therapy (if applicable)	Follow-Up Visit ² (EOT + 2 weeks) (± 2 days)	Long term Follow-Up (EOT + 6 weeks) (± 1 weeks)
Informed consent	X	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-
Complete physical examination (including vital signs) ³	X									
Targeted physical examination (Including vital signs)			X	X	X	Every 3 days ⁴	X	X	X	X
Temperature	X	X ⁴							X	X
Signs and symptoms assessment	X				X		X	X	X	X
Urine or serum pregnancy test ⁵	X ⁵						X ⁵	X ⁵		X ⁵
Dilated fundoscopic exam ⁶	X ⁷						X ⁸	X ⁸	X ⁸	X ⁸
Blood cultures ⁹	X ¹⁰		X	X			X	X	X ¹¹	X ¹¹
Specimen culture ¹²	X	X					X	X	X	X
CBC with differential ¹³	X		X	X		Every 7 Days	X	X	X ¹⁴	X ¹⁴
Serum chemistry ¹³	X		X	X		Every 7 Days	X	X	X ¹⁴	X ¹⁴
Echocardiogram (only for subjects with <i>Candida</i> endocarditis) (not applicable to Korean and Portuguese investigator sites)	X ¹⁵						X ¹⁶	X ¹⁶		
Magnetic Resonance Imaging (MRI) study (only for subjects with <i>Candida</i> osteomyelitis) (not applicable to Korean and Portuguese investigator sites)	X ¹⁷						X ¹⁸	X ¹⁸		

Pharmacokinetic sampling for anidulafungin (first 6 subjects 1 month to <2 yrs old) ¹⁹		Days 1 and 2								
Pharmacokinetic sampling for anidulafungin and polysorbate 80 measurement (all other subjects) ²⁰		Days 1, 3, 5, 7 and 9								
Study medication administration		X								
Adverse events		X					X	X	X	X
Concomitant medications	X ²¹	X							X ²²	X ²²
Evaluation of Clinical and Microbiologic Response ²³							X	X	X	X
Follow up evaluation (relapse [recurrence], new infection, or continued resolution/improvement) ²³									X	X

1. Screening procedures/assessments are to be completed before the first dose of study medication.
2. Follow-up visit (EOT + 2 weeks) is only required in subjects with microbiologically confirmed invasive candidiasis/candidemia (ICC).
3. May occur within 72 hours before the first dose of study medication.
4. Subjects undergoing treatment in the outpatient setting may have less frequent assessments, but not less than once every 7 days. Close monitoring of subjects in the outpatient setting is required.
5. A urine or serum pregnancy test will be performed at screening (prior to treatment initiation), at the end of therapy or at the end of IV therapy, whichever is later, and at the 6-week follow-up visit. Additional testing may also be performed as per request of the IRB/EC or as required by local regulations.
6. Fundoscopic exams should be performed with pupils dilated if possible. In addition, when required by the protocol, the exam should be performed by an ophthalmologist unless it is not possible for practical reasons, in which case it may be performed by the principal investigator or subinvestigator.
7. If it is not possible to perform a baseline fundoscopic examination prior to the first dose of study drug, it may be performed up to 48 hours after the first dose. Under extenuating circumstances, if the fundoscopic examination cannot be performed prior to first dose or within 48 hours, every effort should be made to perform the examination as soon as possible thereafter. Please note, if the baseline fundoscopic examination is positive for findings consistent with *Candida* endophthalmitis, then a repeat fundoscopic examination is required at the end of treatment and at the 2- and 6-week follow-up visits. Additional fundoscopic assessments, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional fundoscopic examinations are performed, the results should be recorded on the case report form.
8. To be completed only if the baseline fundoscopic examination was abnormal.
9. Blood cultures will be obtained on Day 1, prior to the administration of study drug, for all subjects. If a positive culture is returned, repeat cultures are required at least every 3 days until 2 consecutive cultures separated by 24 hours or more are confirmed to be negative. For subjects who are prematurely discontinued from treatment for any reason, a blood sample for culture should be obtained only if it is clinically indicated. For subjects without microbiologically confirmed ICC, further cultures will be drawn at the discretion of the investigator. Pathogen isolated will be documented

in all cases.

10. The 'screening visit culture' is the culture result that qualifies the subject with definitive diagnosis of ICC for study entry (along with other inclusion criteria) and is from a blood or tissue sample that was obtained within 96 hours prior to the screening visit, that is positive for *Candida* sp. The result of this culture will be recorded on the 'screening visit' case report form. In the event the culture result from this sample is pending, plan to record the culture result on the screening visit case report form once the organism has been identified and the information is available. Please note: if the day of the screening visit is also Day 1 of treatment, a sample of blood for culture will be obtained; otherwise a sample of blood for culture is not required until the first day of treatment (Day 1), just prior to administration of study drug.
11. A blood culture at the 2-week and 6-week follow-up visit is required only if clinically indicated.
12. Cultures of other sterile sites will be collected as clinically indicated. Pathogen isolated will be documented.
13. CBC with differential (including RBC count, reticulocytes, white blood cells, neutrophils, lymphocytes, monocytes, basophils, and platelet count), and serum chemistry tests (AST, ALT, Alk-Phos, total Bilirubin, Albumin, BUN or Urea, Cr, Bicarbonate, Glucose, Na, K, Ca, Cl, Mg) are to be repeated on Day 3, 7 and every seven days during treatment phase, and repeated at both follow-up visits.
14. Hematology and chemistry tests should be repeated at both follow-up visits.
15. An echocardiogram at the time of screening is not required if the test was already performed within the previous 96 hours (of the screening visit). The results of the echocardiogram, however, must be recorded in the case report form. (Not applicable to Korean and Portuguese investigator sites.)
16. For subjects with *Candida* endocarditis, either a transesophageal (preferred) or transthoracic echocardiogram must be performed at the end of study treatment (ie, at the end of treatment with IV anidulafungin, or at the end of treatment with oral fluconazole in subjects who are switched to oral therapy). Additional echocardiogram assessments, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional echocardiogram assessments are performed, the results should be recorded on the case report form. (Not applicable to Korean and Portuguese investigator sites.)
17. A magnetic resonance imaging (MRI) study at the time of screening is not required if the test was already performed within the previous 96 hours (of the screening visit). The results of the MRI, however, must be recorded in the case report form. (Not applicable to Korean and Portuguese investigator sites.)
18. For subjects with *Candida* osteomyelitis, a magnetic resonance imaging (MRI) study of the affected area must be performed at the end of study treatment (ie, at the end of treatment with IV anidulafungin, or at the end of treatment with oral fluconazole in subjects who are switched to oral therapy). Additional MRI studies, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional MRI studies are performed, the results should be recorded on the case report form. (Not applicable to Korean and Portuguese investigator sites.)
19. Prior to the administration of the first dose of study drug, a plasma sample (0.1 – 0.2 mL) should be obtained. Excess blood collected for safety laboratory testing may be used for this sample; otherwise it should be collected directly from the subject. Following the initiation of study drug treatment six blood samples (0.3 – 0.5 mL each) will be collected for anidulafungin measurement at the following time points in the first 6 subjects: on Day 1 (receiving 3.0 mg/kg IV infusion); 2 minutes before the end of infusion; on Day 2 (receiving 1.5 mg/kg IV infusion): just prior to the start of the infusion, 2 minutes before the end of infusion, and 6, 12 and 24 hours after the start of infusion. Exact sampling times may be modified to accommodate subject schedules provided the actual time of collection is documented in the Case Report Form (CRF). For the first 6 subjects aged 1 month to <2 years, use of a second systemic antifungal agent (eg, amphotericin B) will be permitted (these subjects will be enrolled at selected centers).
20. Two aliquots of blood samples (one: approximately 0.3 - 0.5 mL for anidulafungin measurement; the other: approximately 1 mL for polysorbate 80 [the excipient in the formulation] measurement) will be collected at 3-5 of the following occasions during the study: Day 1: Post-dose (between 0-2 hours following the end of anidulafungin infusion); Day 3: Pre-dose (just prior to the start of anidulafungin infusion); Day 5: Post-dose (between

0-3 hours following the end of anidulafungin infusion); Day 7: Delayed post-dose (between 6-12 hours following the end of anidulafungin infusion); Day 9: Pre-dose (just prior to the start of anidulafungin infusion). Exact sampling times may be modified to accommodate subject schedules as long as the samples are collected during the IV treatment period. If only 3 samples can be collected, preference is for the two post-dose and one delayed post-dose time points. The delayed post-dose sample may be collected prior to Day 7, for example on Day 3, to facilitate the preferred sample collection.

21. Only antifungal medications the subject has received within the past 30 days prior to enrolment are required to be recorded.
22. Only antifungal medications and their indication for use (eg, for prophylaxis or treatment) are required to be reported during the follow-up period unless the subject experiences an adverse effect during this time, in which case all concomitant medications the subject was receiving at the time of the adverse event must be recorded.
23. These efficacy assessments will be completed only in subjects with microbiologically confirmed ICC.

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1. INTRODUCTION

On 17 February 2006, the US FDA approved intravenous (IV) anidulafungin in adults for treatment of candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) at a dose of 100 mg daily (an initial loading dose of 200 mg), and for the treatment of esophageal candidiasis, at a dose of 50 mg daily (an initial loading dose of 100 mg).

On 26 September 2007, the European Union (EU) European Medicines Agency (EMA) approved IV anidulafungin in adult, non-neutropenic patients for the treatment of invasive candidiasis, with a recommended dose of 100 mg (an initial loading dose of 200 mg).

On 14 November 2007, Health Canada approved IV anidulafungin for the treatment of invasive candidiasis/candidemia in adult non-neutropenic patients.

1.1. Indication

In this protocol, anidulafungin is being studied for treatment of invasive candidiasis, including candidemia, in children between the ages of 1 month and <18 years.

1.2. Background and Rationale

The incidence of systemic invasive fungal infections has risen significantly in the past decade. Infections due to *Candida* spp. account for about 80% of all systemic fungal infections and are the fourth leading cause of all nosocomial bloodstream infections in the United States.¹ The impact of fungal infections on health care and economic expenditures is large and of growing concern. Increases in infection rates are a consequence of growing numbers of at-risk patients due to advances in transplantation technology and oncology treatment, spread of the Human Immunodeficiency Virus (HIV), use of vascular catheters, and extensive administration of broad-spectrum antibiotics.

In the United States, mortality rates in children with candidemia approach 30%, depending on the specific patient population and clinical setting.^{2,3} Current approved treatments for infections due to *Candida* spp. include polyenes, azoles and echinocandin antifungal agents. Of these, amphotericin B and fluconazole are the most commonly utilized in the paediatric population. Guidelines for use of these agents in the paediatric population have often been extrapolated from adult studies.

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 candidemia 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 ICC. Exposure-response relationships of anidulafungin will also be assessed in a population pharmacokinetic-pharmacodynamic (PK-PD) analysis.

Additionally, due to the lack of excipient exposure/response data of polysorbate 80 in very young children (eg, < 2 years of age), the Paediatric Committee (PDCO) at the European Medicines Agency requested to measure plasma levels of the excipient polysorbate 80, a solubilizing agent contained in the intravenous (IV) formulation of anidulafungin. Thus, pharmacokinetics of polysorbate 80 will also be explored.

1.3. Overview of Anidulafungin

Anidulafungin is a semi-synthetic lipopeptide synthesized from a fermentation product of *Aspergillus nidulans*. It acts as a non-competitive inhibitor of (1,3)- β -D-glucan synthase, an enzyme required for synthesis of the cell wall in many pathogenic fungi. Suppression of cell wall glucan synthesis leads to osmotic instability and eventual cell death.

1.3.1. Pre-Clinical Data

Anidulafungin is active in vitro against a number of important pathogenic organisms, including *Candida* spp., *Aspergillus* spp., and *Pneumocystis jiroveci* (formerly *P. carinii*). It is at least as potent as and often more potent than amphotericin B and fluconazole against *Candida* and *Aspergillus* spp. Activity of anidulafungin against *Candida* spp is fungicidal and has been demonstrated under a variety of growth conditions.

In animal models, anidulafungin has cleared *Candida* from internal organs and mucosa and led to prolonged survival in lethal infections. Anidulafungin demonstrated efficacy in studies in immunosuppressed and immunocompetent mice systemically infected with *C. albicans* or *C. glabrata* (including fluconazole- and amphotericin B-resistant isolates), immunosuppressed rabbits with fluconazole-resistant esophageal and oropharyngeal candidiasis, and persistently neutropenic rabbits with disseminated *C. albicans* candidiasis.

1.3.2. Clinical Data

Clinical Pharmacology

Anidulafungin exhibits linear and predictable pharmacokinetics. The pharmacokinetic profile of anidulafungin following IV administration is characterized by a short distribution half-life ($t_{1/2,\alpha}$) of 0.5-1 hour, a predominant elimination half-life ($t_{1/2,\beta}$) of approximately 24 hours that characterizes the majority of the concentration-time profile, and a terminal elimination half-life ($t_{1/2,\gamma}$) of 40-50 hours. Steady state is achieved on the first day after a loading dose (twice the daily maintenance dose). Anidulafungin is extensively bound to human plasma proteins (>99%).

Anidulafungin undergoes slow chemical degradation to produce a ring-opened peptide that lacks antifungal activity, which is subsequently converted to peptidic degradants and eliminated in feces. Anidulafungin has negligible renal clearance (<1%). It is not a clinically relevant substrate, inducer, or inhibitor of cytochrome P450 enzymes. No clinically relevant drug-drug interactions were observed when anidulafungin was co-administered with cyclosporine, voriconazole, tacrolimus, amphotericin B or rifampin. Dose adjustments are not required for subjects with any degree of hepatic or renal insufficiency, nor are they required on the basis of age, gender, weight, ethnicity, disease status, or concomitant medications.

In the paediatric population, pharmacokinetic profiles were assessed in a Phase 1/2 multicenter, open-label, sequential dose-escalation study (from 0.75 mg/kg/day to 1.5 mg/kg/day) of IV anidulafungin administered as early empirical therapy to 24 immunocompromised children ages 2 to 17 years with neutropenia. Children were stratified by age, from 2 to 11 years and from 12 to 17 years. There was no relationship between subject age and the peak concentration (C_{max}), area under curve over dosing interval (AUC_{24}), weight-normalized clearance (CL), or weight-normalized steady-state volume of distribution (V_{ss}). The pharmacokinetic profiles on a weight-adjusted basis of 0.75 and 1.5 mg/kg/day were similar to the profiles of anidulafungin administered to adults at dosages of 50 and 100 mg/day, respectively.

The pharmacokinetics of anidulafungin have not yet been characterized in subjects less than 2 years of age. Based upon prior studies and the pharmacokinetic properties of anidulafungin (eg, linear pharmacokinetics, minimal renal elimination and no hepatic metabolism), it is anticipated that the dose to be used in this age group will be the same as that of subjects aged 2-17 years. In this study, the pharmacokinetics of anidulafungin will be studied in the first 6 subjects between 1 month to <2 years of age to confirm the dosing regimen in this age group. For all other subjects, sparse pharmacokinetic samples will be collected to explore the relationship between anidulafungin exposure and response using a population PK-PD analysis approach, including exploring the association between PK-PD index (eg, $AUC/\text{minimum inhibitory concentration (MIC)}$) and efficacy endpoints.

Efficacy in Invasive Candidiasis, including Candidemia (Adults)

Anidulafungin was compared to fluconazole in a pivotal Phase 3, double-blind, randomized study of subjects aged 16 years and above with candidemia and other forms of invasive candidiasis. Subjects received either IV anidulafungin (200-mg on Day 1 and 100 mg daily thereafter) or IV fluconazole (800 mg on Day 1 and 400 mg daily thereafter, with dosage adjustment as necessary for renal insufficiency) for 14 to 42 days. Subjects in either arm could be switched to oral fluconazole (400 mg) after at least 10 days of IV treatment if protocol-specified criteria were met. There were 256 subjects in the Intent to Treat (ITT) population, of whom 131 received IV anidulafungin and 125 received IV fluconazole. In the primary efficacy analysis of global response (ie, microbiologic and clinical response) at the End of IV Therapy (EOIVT) in the Modified-ITT population, 75.6% of subjects randomized to anidulafungin had a successful response, compared to 60.2% for subjects randomized to fluconazole (95% CI 3.85, 26.99).

Fewer anidulafungin-treated subjects (30 [22.9%]) than fluconazole-treated subjects (39 [31.2%]) died during and shortly after the study. At almost all time points throughout the study, the probability of survival for anidulafungin-treated subjects was higher than for fluconazole-treated subjects. For subjects who died, the median time to death was 14 days for fluconazole and 21 days for anidulafungin. In subjects with forms of invasive candidiasis other than lone candidemia, 8 of 11 (72.7%) who received anidulafungin were considered global successes at the EOIVT compared with 8 of 15 (53.3%) subjects in the fluconazole group.

Safety

The safety of anidulafungin has been assessed in 929 subjects, including 672 subjects in Phase 2/3 studies. Treatment-related adverse events that were reported in $\geq 2\%$ of subjects in the pivotal Phase 3 comparative candidemia and other forms of invasive candidiasis study in adults included diarrhea, increased alkaline phosphatase and hypokalemia.⁴

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Anidulafungin Investigator Brochure.⁵

1.4. Overview of Fluconazole

Fluconazole is an azole antifungal agent used in the treatment of infection due to *Candida* sp. Information regarding the approved indications for fluconazole can be found in the manufacturer's approved product labeling. Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Fluconazole Core Data Sheet.⁶

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary

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

Secondary

- 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;
- To explore pharmacokinetic parameters of anidulafungin in children aged 1 month to <2 years following IV infusion of anidulafungin (AUC_{24} and C_{max});
- To explore pharmacokinetic parameters of polysorbate 80 following IV infusion of anidulafungin (AUC_{24} and C_{max});
- 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;
- To assess rates of relapse (recurrence) at the Week 2 and Week 6 FU visits;
- To assess rates of new infection at the Week 2 and Week 6 FU visits;
- To assess all-cause mortality during study therapy and Follow-Up visits.

2.2. Endpoints

Primary Endpoint

- The primary endpoint will be an assessment of the safety and tolerability of anidulafungin.

Secondary Endpoints

- Global response (based on the clinical and microbiological responses) at the EOIVT, EOT, Week 2 and Week 6 FU visits;
- Pharmacokinetic parameters of anidulafungin in children aged 1 month to <2 years following IV infusion of anidulafungin: AUC₂₄ and C_{max};
- Pharmacokinetic parameters of polysorbate 80 following infusion of anidulafungin: AUC₂₄ and C_{max};
- Exposure-response (efficacy and safety endpoints) relationships of anidulafungin using a nonlinear mixed effects approach as appropriate;
- Rates of relapse (recurrence) at the Week 2 and Week 6 FU visits;
- Rates of new infection at the Week 2 and Week 6 FU visits;
- All-cause mortality during study therapy and Follow-Up visits.

3. STUDY DESIGN

This prospective, open-label, non-comparative study will assess the pharmacokinetics, 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 discontinue study treatment but will remain in the study for continued safety monitoring for up to 6 weeks after the last dose of study treatment.

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. Enrollment will be stratified by age (1 month - <2 years, 2 - <5 years, and 5 - <18 years), allowing 20 ± 2 in each stratum.

Subjects with microbiologically confirmed ICC may be switched to oral fluconazole (6-12 mg/kg/day, maximum 800 mg/day) after at least 10 days of IV anidulafungin treatment, provided that all of the following criteria are met:

- The subject is afebrile for at least 24 hours;
- The subject is able to tolerate oral medication;
- Documentation of two blood cultures negative for *Candida* spp separated by at least 24 hours;
- Eradication or presumed eradication of *Candida* sp. from any other sites of infection identified at enrollment;
- The specific *Candida* isolate identified at study entry is susceptible (or presumed to be susceptible based on the species identified and local *Candida* sp. resistance patterns) to fluconazole;
- Signs and symptoms of *Candida* infection have improved such that the Investigator feels it is appropriate to switch to oral fluconazole.

Subjects will receive treatment (either solely IV anidulafungin, or anidulafungin followed by oral fluconazole) for a minimum duration of 14 days from the time of the last of 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 symptoms 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.

The maximum total treatment duration for all subjects in this study is 49 days, and the maximum allowed treatment duration with anidulafungin is 35 days. The last day of study treatment will be considered the End of Treatment (EOT). It is expected that the majority of subjects will receive study drug in the hospital; subjects will be permitted to complete study medication on an outpatient basis if deemed appropriate by the investigator.

(This paragraph, as it relates to subjects with Candida endocarditis and Candida osteomyelitis is not applicable to Korean and Portuguese investigator sites.) 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.

All subjects enrolled in the study who receive at least one dose of study drug treatment, including those subjects who are discontinued from treatment (regardless of the reason), will be followed for a total of 6 weeks after EOT (ie, the last dose of study drug treatment) and are required to return for the 2-week and 6-week follow-up visit.

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine or serum pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. If a positive culture is returned, repeat blood cultures are required at least every 3 days until 2 cultures separated by 24 hours or more are confirmed to be negative. For subjects without microbiologically confirmed ICC, further cultures will be drawn at the discretion of the investigator.

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. These subjects may be administered anidulafungin in one of two ways: either as monotherapy or in combination with a second systemic antifungal agent (eg, amphotericin B).

If the investigator chooses to administer anidulafungin as monotherapy for the treatment of invasive candidiasis/candidemia, then treatment will be administered 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.

In the event the investigator chooses to administer anidulafungin in combination with a second antifungal agent, anidulafungin will be discontinued following the obtainment of required blood samples for pharmacokinetic analysis as specified by the protocol; the data from these subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. After the dosing regimen is confirmed by the Sponsor, enrollment will be opened to additional subjects within this age group at all investigator sites. Subsequent to this time point, the use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted in any subject.

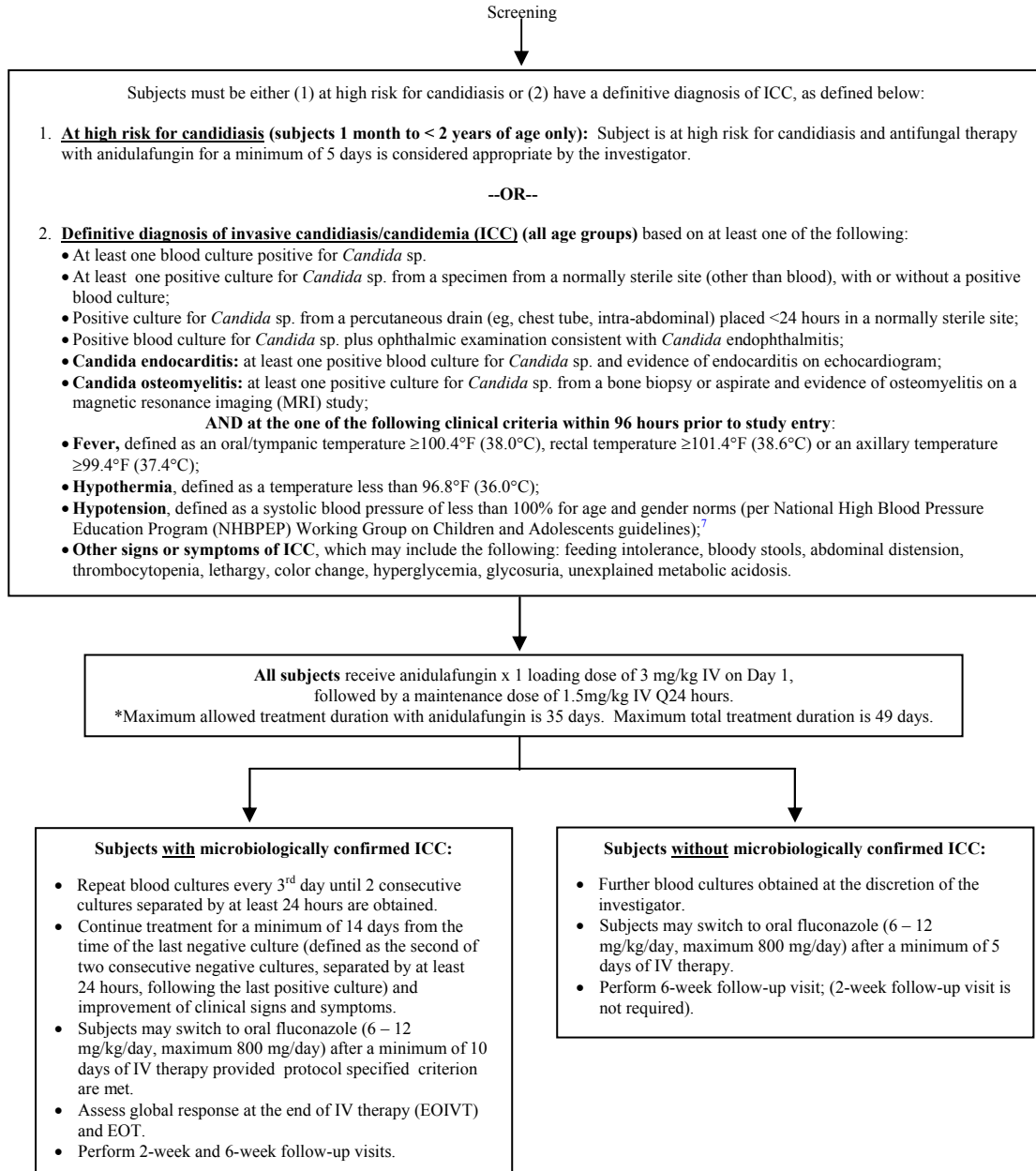
A population PK-PD analysis will also be performed in all other subjects enrolled and will include subjects <2 years of age who are not part of the 6 subject cohort described above, in which 3 to 5 sparse pharmacokinetic samples will be collected. Additionally, at the request of PDCO, pharmacokinetics of polysorbate 80, a solubilizing agent contained in the IV formulation of anidulafungin, will also be explored.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure 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.

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

Study Schematic:

(Korea and Portugal: *Inclusion criteria related to Candida endocarditis or Candida osteomyelitis not applicable to Korean and Portuguese investigator sites.*)



4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Subject must be either (1) at high risk for candidiasis or (2) have a definitive diagnosis of invasive candidiasis/candidemia (ICC), as defined below:
 - a. **At high risk for candidiasis (subjects 1 month to < 2 years of age only):**
Subject is at high risk for candidiasis and antifungal therapy with anidulafungin for a minimum of 5 days is considered appropriate by the investigator.

--OR--

- b. **Definitive diagnosis of invasive candidiasis/candidemia (ICC) (all age groups)**
is based on the growth of *Candida* sp. from a blood and/or tissue culture obtained from a normally sterile site.

For the purpose of study entry, a subject enrolled with definitive diagnosis of ICC must have at least one microbiologic AND at least one clinical criterion listed below.

Microbiologic Criteria:

Subject must have at least one of the criteria listed below either at the time of study entry or within 96 hours prior to study entry.

- **Candidemia:** At least one blood culture positive for *Candida* sp. (in the absence of other demonstrated foci of infection) or;
- Other forms of invasive candidiasis:
- Positive culture for *Candida* sp. from a specimen from a normally sterile site (other than blood), with or without a positive blood culture;
- Positive culture for *Candida* sp. from a percutaneous drain (eg, chest tube, intra-abdominal) placed <24 hours in a normally sterile site;

- Positive blood culture for *Candida* sp. plus ophthalmic examination consistent with *Candida* endophthalmitis;
- **Candida endocarditis** (*not applicable to Korean and Portuguese investigator sites*): At least one positive blood culture for *Candida* sp. and evidence of endocarditis on echocardiogram;
- **Candida osteomyelitis** (*not applicable to Korean and Portuguese investigator sites*): At least one positive culture for *Candida* sp. from a bone biopsy or aspirate and evidence of osteomyelitis on a magnetic resonance imaging (MRI) study;

Clinical Criteria:

Subject must have at least one of the criteria listed below either at the time of study entry or within 96 hours prior to study entry.

- **Fever**, defined as an oral/tympanic temperature $\geq 100.4^{\circ}\text{F}$ (38.0°C), rectal temperature $\geq 101.4^{\circ}\text{F}$ (38.6°C) or an axillary temperature $\geq 99.4^{\circ}\text{F}$ (37.4°C);
- **Hypothermia**, defined as a temperature less than 96.8°F (36.0°C);
- **Hypotension**, defined as a systolic blood pressure of less than 100% for age and gender norms (per National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents guidelines);⁷
- **Other signs or symptoms of candidemia/invasive candidiasis**, which may include the following: feeding intolerance, bloody stools, abdominal distension, thrombocytopenia, lethargy, color change, hyperglycemia, glycosuria, unexplained metabolic acidosis.

**** Important Notes ****

Subjects may be enrolled in the study and initiate study treatment on the basis of mycologic 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 (eg, blood and/or tissue). If culture confirmation of *Candida* sp. 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 discontinued treatment but will remain in the study for continued safety monitoring for up to 6 weeks after the last dose of study treatment. Refer to [Section 6.5](#) and [Section 6.6](#) for follow-up visit requirements.

Positive cultures for *Candida* sp. from urine (in the absence of clinical signs and symptoms of pyelonephritis), sputum, bronchoalveolar lavage (BAL),

endotracheal aspiration, gastric drainage or gastric aspiration do not qualify as a positive culture for definitive diagnosis of ICC.

2. Male or female between the ages of 1 month and <18 years.
3. Male and female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the treatment period and up to the 6 week follow-up visit. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.
4. For each subject, parent or legal guardian must be willing and able to provide signed and dated written informed consent documentation. Assent from the child or adolescent will be obtained as appropriate. This is to be obtained prior to enrollment.
5. Will be available for the duration of the study and be able to abide by the study restrictions.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.
2. Premature neonates born at gestation of less than 36 weeks (unless the sum of gestational age plus chronological age is at least 44 weeks).

Note: Rounding to the closest week is round up one week if birth occurred on days 4 to 6 of the week and round down one week if birth occurred on Days 1 to 3 of the week.
3. Known history of intolerance, allergy, hypersensitivity or serious reaction to anidulafungin or any of its excipients (including fructose), or to other echinocandin antifungals.
4. Pregnant females; breastfeeding females; males and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception during the treatment period and up to the 6 week follow-up visit.
5. Subjects who have failed antifungal therapy with any systemic echinocandin for this episode of candidiasis/candidemia. Recurrence within 2 weeks is considered failure of previous therapy.
6. Subjects with any of the following abnormal laboratory values: Total bilirubin, AST or ALT >5 times the upper limit of normal (ULN).

7. Subjects who require continued treatment with another systemic antifungal agent [oral nonabsorbable azoles (eg, clotrimazole troches) will be permitted]. Exception: the first 6 subjects enrolled who are between 1 month to <2 years of age may receive a second systemic antifungal agent at the investigator's discretion.
8. Subjects with poor venous access that would preclude IV drug delivery or multiple blood draws.
9. Subjects who have participated in a study of an investigational drug or device (without any FDA and EMEA approved indications) within four weeks of study entry. The investigational use of licensed agents are permitted if the subject is on a stable regimen for four weeks prior to study start, and expected to remain on the stable regimen for the duration of the trial.
10. Life expectancy <72 hours.
11. Subjects with suspected *Candida* meningitis. **(For Korean and Portuguese investigator sites only:** Subjects with suspected *Candida* endocarditis and *Candida* osteomyelitis are also excluded.)
12. Subjects with 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 or in situations where catheter salvage is desirable due to the subject's clinical condition.

**** Important Note ** If it is anticipated that a prosthetic device or vascular catheter cannot be removed, the medical monitor should be contacted to discuss enrolment.**
13. Subjects with a vascular graft suspected to be the site of the *Candida* infection and positive blood cultures.
14. Subjects with prosthetic or native valve *Candida* endocarditis who have not and/or cannot undergo valvular replacement surgery prior to or soon after study entry. **(Not applicable to Korean and Portuguese investigator sites.)**
15. Subjects with *Candida* osteomyelitis associated with a prosthetic device in whom the prosthetic device has not been and/or cannot be removed surgically prior to or soon after study entry. **(Not applicable to Korean and Portuguese investigator sites.)**
16. Other severe acute or chronic medical or psychiatric condition, electrocardiogram (ECG) abnormalities, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.3. Randomization Criteria

This is a non-randomized study. The first day study treatment will be Day 1.

4.4. Life Style Guidelines

It is expected that the majority of subjects will receive study drug in the hospital; subjects will be permitted to complete study medication on an outpatient basis if deemed appropriate by the investigator.

All male subjects who are able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and up to the 6 week follow-up visit. The investigator or his or her designee, in consultation with the subject, will select the most appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below), and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. The investigator or his or her designee, at each study visit, will confirm and document consistent and correct use. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation or bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

6. Female partner who meets the criteria for non-childbearing potential, as described below:

Female subjects of non-childbearing potential must meet at least one of the following criteria:

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or
- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

Complete abstinence may be considered an acceptable method of contraception on a case-by-case basis with Pfizer's concurrence prior to performing any screening tests or procedures for the study. This decision and Pfizer's concurrence should be documented in the subject's source record.

4.5. Central Venous Catheter Management

Because *Candida* species adhere avidly to materials used in vascular catheters, catheter removal is strongly recommended in the management of candidemia. The date the suspected infected intravascular catheter was inserted and removed will be recorded in the Case Report Form (CRF). The insertion of any new intravascular catheters, including changing catheters over a guide-wire will also be documented on the non-pharmacological treatment procedure record. Any cultures that were done on the tip of the catheter or site of the catheter insertion will be recorded in the CRF.

4.6. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the investigator site file.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace,

the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

This study is open-label and all subjects will receive anidulafungin. The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

Eligible subjects will be considered enrolled into the study provided they have satisfied all entry criteria and a legal representative has provided consent. Subjects will be assigned a subject number at the time of screening. This identifying number will be retained for the subject throughout the duration of study participation and must be used on all correspondence and documentation.

The Principal Investigator is responsible for ensuring that the subject is eligible for the study.

All subjects will receive IV anidulafungin. For dosing purposes younger subjects must be weighed frequently (such as daily), but less frequently for older children as determined by the investigator. 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.

After a minimum of 10 days of treatment with IV anidulafungin, subjects with microbiologically confirmed ICC may be switched to oral fluconazole (6 – 12 mg/kg/day, maximum 800 mg/day) provided that all of the following criteria are met:

- The subject is afebrile for at least 24 hour;
- The subject is able to tolerate oral medication;
- Documentation of two blood cultures negative for *Candida* spp separated by at least 24 hours;
- Eradication or presumed eradication of *Candida* sp. from any other sites of infection if identified at enrollment;
- The specific *Candida* isolate identified at study entry is susceptible (or presumed to be susceptible based on the species identified and local *Candida* sp. resistance patterns) to fluconazole;
- Signs and symptoms of *Candida* infection have improved such that the Investigator feels it is appropriate to switch to oral fluconazole.

Treatment will continue 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 symptoms 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.

The maximum total treatment duration for all subjects in this study is 49 days, and the maximum allowed treatment duration with anidulafungin is 35 days. The last day of study treatment will be considered the EOT. Subjects will be followed in the study for a total of 6 weeks after EOT. It is expected that the majority of subjects will receive study drug in the hospital; subjects will be permitted to complete study medication on an outpatient basis if deemed appropriate by the investigator.

(The following two paragraphs are not applicable to Korean and Portuguese investigator sites.)

**** Important Note for Subjects with *Candida* Endocarditis and *Candida* Osteomyelitis****

The maximum total treatment duration in this study is 49 days, and the maximum allowed treatment duration with anidulafungin is 35 days. After at least 10 days of treatment with anidulafungin, subjects may be switched to oral fluconazole (provided switch criteria are met) to complete 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.

5.2. Drug Supplies

5.2.1. Formulation and Packaging

Study Drug

Generic Name:	Anidulafungin
Trade Name:	Eraxis™/Ecalta®
Dosage Form:	Intravenous
Strength:	100 mg

Manufacturer: Pfizer Inc.

Clinical Supply

Packaging: Anidulafungin (Eraxis™/Ecalta®) for Injection will be supplied as an investigational product by the Pfizer Supply Chain. Anidulafungin for injection will be packaged and labeled to meet study-specific and regulatory requirements. Written Dosing Administration Instructions (DAI) will be provided that describe the method for reconstitution and further dilution of anidulafungin in preparation for administration.

Each participating site is responsible to provide the Water for Injection (WFI), USP in order to reconstitute the lyophilized anidulafungin. Each site is also responsible to provide the necessary intravenous solutions required to further dilute the reconstituted anidulafungin for administration by IV infusion. Refer to the Dosing Administration Instructions for detailed instructions on dose preparation.

Oral Medication

Generic Name: Fluconazole

Dosage Form: Oral tablets and oral suspension

Strength: Oral tablets containing 50, 100, 150, or 200 mg of fluconazole.

Oral Suspension containing 10 mg/mL, 40 mg/mL or 50 mg/mL of fluconazole.

Manufacturer: Pfizer Inc. or generic manufacturer

Clinical Supply

Packaging: Each participating site is responsible to procure commercially packaged fluconazole tablets and oral suspension as needed.

Note: If applicable, the site can use the locally available capsule formulation of fluconazole.

5.2.2. Preparation and Dispensing

Written Preparation and Administration Instructions will be provided to each investigative site by the sponsor. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance. Anidulafungin lyophile will be reconstituted with water for injection. Please refer to the Dosage and Administration Instructions for preparation and administration of anidulafungin intravenous solution.

5.2.3. Administration

Anidulafungin will be administered intravenously at an infusion rate not exceeding 1.1 mg/minute. Anidulafungin loading dose of 3.0 mg/kg (not to exceed 200 mg) on the first day of treatment should be administered intravenously at a rate of 1.1 mg/min or less, however the actual duration of infusion time should not exceed the calculated duration of infusion time (based on 1.1 mg/min) plus an additional 30 minutes. For example, for a child weighing 25 kg, the calculated duration of infusion time (based on a rate of 1.1 mg/min) would be 68 minutes, and maximum duration of infusion would be 98 minutes (68 minutes plus 30 minutes).

Anidulafungin maintenance dose of 1.5 mg/kg/day (not to exceed 100 mg) on subsequent days should be administered intravenously at a rate of 1.1 mg/min or less, however the actual duration of infusion time should not exceed the calculated duration of infusion time (based on 1.1 mg/min) plus an additional 30 minutes. For example, for a child weighing 25 kg, the calculated duration of infusion time (based on a rate of 1.1 mg/min) would be 34 minutes, and maximum duration of infusion would be 64 minutes (34 minutes plus 30 minutes).

**** Important Note ** In subjects who already initiated on IV anidulafungin prior to study entry, a repeat loading dose is not required. Instead, these subjects may be initiated on maintenance doses of IV anidulafungin.**

5.2.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong drug, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the CRFs and on the Serious Adverse Event (SAE) form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page (refer to [ADVERSE EVENT REPORTING](#) section for further details).

5.2.5. Compliance

It is expected that the majority of the subjects will receive study drug in the hospital setting. In this case, compliance with IV and oral therapy administered during hospitalization will be assessed by the Study Monitor during site visits, and by the sponsor upon review of the study data at the end of the study.

Subjects who are switched to oral treatment and discharged from the hospital will be provided with a known quantity of oral study medication for continued therapy in the outpatient setting. Appropriate drug accountability measures should be implemented to appropriately evaluate compliance. Subjects should also be interviewed regarding adherence to treatment.

5.3. Drug Storage and Drug Accountability

Investigational product should be stored in its original container and in accordance with the label. Detailed information regarding Drug Storage will be provided by the sponsor to each investigative site with the Written Dosing Administration Instructions. Refer to the Dosing Administration Instructions for detailed instructions regarding dose storage. Storage conditions stated in the single reference safety document (SRSD) (eg, investigator's brochure [IB]), will be superseded by the storage conditions stated in the labeling.

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area, under required storage conditions and in accordance with applicable regulatory requirements.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

The investigator, or approved representative (eg, pharmacist) must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product(s). When investigational product is taken home by the subject, all unused products must be returned to the investigator by the subject at the follow-up visit. Pfizer may supply drug accountability forms that must be used or may approve use of standard institution forms. In either case, the forms must identify the investigational product, including batch or code numbers, and account for its disposition on a subject-by-subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to Pfizer.

Pfizer or designee will provide instructions as to destruction of any unused investigational product. If Pfizer authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented.

5.4. Concomitant Medication(s)

Any medication that the subject takes other than the study drug specified in the protocol is considered concomitant medication. Information about concomitant medications will be recorded in the Case Report Form (CRF) from the screening visit through the EOT.

At the 2-week and 6-week FU Visits, only antifungal therapy the subject receives and the indication for use (eg, prophylaxis, treatment) will be recorded in the CRF. The use of non-absorbable antifungal drugs (eg, clotrimazole troches) is not required to be reported.

The recording of concomitant medications other than antifungal agents at these time points is not required unless the subject experiences an adverse event during the follow-up period, in which case all concomitant medications that the subject was receiving at the time of the adverse event must be recorded.

Treatment with another systemic antifungal agent [aside from oral nonabsorbable azoles (eg, clotrimazole troches) is not permitted, with the following exception: for the PK sub-study only (first 6 subjects aged 1 month to <2 years) administration of a second medication classified as an azole, polyene, or echinocandin will be allowed during the study treatment phase, at the Investigator's discretion.

6. STUDY PROCEDURES

It is expected that all subjects will be hospitalized at the time study treatment is initiated, and will therefore be under continuous medical surveillance during the early period (if not all) of therapy.

Witnessed written parental or legal guardian consent and assent from the child or adolescent must be obtained prior to performing any screening procedures. Subject identification numbers will be assigned sequentially as subjects are screened into the study and these numbers will be retained throughout the study.

6.1. Screening Visit

The following screening activities will be performed following the informed consent and within two days prior to first dose.

- Obtain informed consent/assent (Note: no study procedures may be performed prior to obtaining written informed consent);
- Medical, surgical, and medication history (Please note: only antifungal medications that the subject was receiving within the past 30 days prior to enrolment are required to be recorded);
- Complete physical examination (including vital signs);
- Temperature;
- Assessment of signs and symptoms of *Candida* infection;
- Urine or serum pregnancy test (for females of childbearing potential);
- Fundoscopic examination;

**** Please Note **** Fundoscopic examination should be performed with pupils dilated if possible. In addition, when required by the protocol, the exam should be performed by an ophthalmologist unless it is not possible for practical reasons, in which case it may be performed by the principal investigator or subinvestigator. If it is not possible to perform a fundoscopic examination prior to the first dose of study drug, it may be performed within 48 hours of the first dose. Under extenuating circumstances, if a fundoscopic examination cannot be performed at baseline or within 48 hours, every effort should be made to perform the examination as soon as possible thereafter.

- Record screening blood and/or tissue (as clinically indicated) culture results (Note: If organism identity is pending, plan to record results on the case report form at a later time when the organism identity is determined and the results are available);
- Obtain blood sample for blood culture if the day of the screening visit is also Day 1 of treatment. Otherwise, a blood sample for blood culture is not required until the first day of treatment (Day 1), just prior to the administration of study drug;
- CBC with differential (Complete blood count with differential and RBC count with reticulocyte count and platelets count);
- Serum chemistry [Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline-Phosphatase (Alk-Phos), Total Bilirubin, Albumin, Bicarbonate, Glucose, Urea nitrogen (BUN), Creatinine (Cr), Sodium (Na), Potassium (K), Calcium (Ca), Chloride (Cl), and Magnesium (Mg)].

- For subjects with *Candida* endocarditis (not applicable to Korean and Portuguese investigator sites): Perform echocardiogram, either transesophageal (preferred) or transthoracic;

**** Please Note **** If an echocardiogram was already performed within the previous 96 hours (of the screening visit), then an echocardiogram at the time of screening is not required. In this case, the results of the echocardiogram used to support the diagnosis of *Candida* endocarditis will be reported in the case report form.

- For subjects with *Candida* osteomyelitis (not applicable to Korean and Portuguese investigator sites): Perform magnetic resonance imaging (MRI) study of affected area;

**** Please Note **** If an MRI was already performed within the previous 96 hours (of the screening visit), then an MRI at the time of screening is not required. In this case, the results of the MRI used to support the diagnosis of *Candida* osteomyelitis will be reported in the case report form.

It is noted that that it may be possible for the screening activities AND Day 1 (first day of study administration) to be the same day. This will be permitted in this protocol.

6.2. Study Period

6.2.1. Daily, Through End of Treatment

- Study drug administration: a loading dose of 3.0 mg/kg (not to exceed 200 mg) on Day 1, and a maintenance dose of 1.5 mg/kg (not to exceed 100 mg) subsequently;
- Record temperature (Note: Subjects receiving treatment in the outpatient setting may have less frequent assessments, but not less than at least once every 7 days. Close monitoring of subjects treated in the outpatient setting is required);
- Record Adverse Events and Concomitant Medications;
- Cultures of other normally sterile sites as clinically indicated.

6.2.2. Days 1 and 2 ONLY for Sub-study Subjects (first 6 subjects aged 1 month to <2 years at selected sites)

Prior to the administration of the first dose of study drug, a plasma sample (0.1 – 0.2 mL) should be obtained and sent to the reference laboratory to test for assay interference. Excess blood collected for safety laboratory testing may be used for this sample, otherwise it should be collected directly from the subject.

Pharmacokinetic sampling: Six (6) blood samples (0.3-0.5 ml each to provide 0.1 – 0.2 mL plasma) will be collected for anidulafungin measurement at the following time points:

- **On Day 1:** 2 minutes before the end of infusion;

- **On Day 2:** Just prior to the start of infusion; 2 minutes before the end of infusion, 6 hours after start of infusion, 12 hours after start of infusion, and 24 hours after start of infusion.
- In the event that the sample required 2 minutes before the end of infusion was not taken at the specified time, every effort must be made to acquire a sample within 5 minutes of the end of infusion with proper and specific time documentation.

Note: In case the subjects are not ready for serial pharmacokinetic sampling on this specific day, this can be re-arranged at a later date when they continue to receive 1.5 mg/kg daily maintenance dose of anidulafungin. The flexibility of the sampling time is also allowed as long as the actual time of collection is recorded in the CRF.

Ideally, the pharmacokinetic (PK) sampling would be taken from a different site/line than the one used for study drug infusion. However, at the discretion of the investigator and with appropriate flushing of the line to clear all drug residues, samples may be collected using the same line.

**** Important Note **** For subjects in whom the investigator has chosen to administer anidulafungin in combination with a second antifungal agent, these subjects will be discontinued from treatment following completion of pharmacokinetic sampling but will remain in the study for continued safety assessments and are required to return for the 2-week and 6-week follow-up visits.

For subjects in whom the investigator has chosen to administer anidulafungin as monotherapy, following completion of pharmacokinetic sampling these subjects will continued to be treated with anidulafungin 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.

6.2.3. Days 1, 3, 5, 7 and 9 for ALL Subjects OTHER Than the Sub-Study Subjects Above

- Pharmacokinetic sampling for anidulafungin and polysorbate 80 measurements: Two aliquots of blood samples (one: approximately 0.3 - 0.5 mL for anidulafungin measurement; the other: approximately 1 mL for polysorbate 80 [a formulation excipient] measurement) will be collected at 3 – 5 of the following occasions during the study:
 - **Day 1:** post-dose (between 0 – 2 hours following the end of anidulafungin infusion);
 - **Day 3:** pre-dose (just prior to the start of the anidulafungin infusion);
 - **Day 5:** post-dose (between 0 – 3 hours following the end of anidulafungin infusion);

- **Day 7:** delayed post-dose (between 6 – 12 hours following the end of anidulafungin infusion);
- **Day 9:** pre-dose (just prior to the start of anidulafungin infusion).

Note: The above sampling days are flexible and could be modified at the discretion of each study center as long as samples are collected between Day 1 and the last day of IV treatment with anidulafungin with the actual time of collection documented in the CRF. If only 3 samples can be collected, preference is for the two post-dose and one delayed post-dose time points. The delayed post-dose sample may be collected prior to Day 7, for example on Day 3, to facilitate the preferred sample collection.

6.2.4. Day 3

- Targeted physical examination (including vital signs);
- Blood cultures (unless two consecutive blood cultures, separated by at least 24 hours, has been confirmed to be negative) (for subjects with microbiologically confirmed ICC);
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening).

6.2.5. Day 7

- Targeted physical examination (including vital signs);
- Blood cultures (unless two consecutive blood cultures, separated by at least 24 hours, has been confirmed to be negative) (for subjects with microbiologically confirmed ICC);
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening).

6.2.6. Day 10

- Targeted physical examination (including vital signs);
- Assessment of signs and symptoms of *Candida* infection.

6.2.7. Days 11 to 34 (Day Prior to Last Day of IV Anidulafungin Therapy – Maximum is 35 Days on Anidulafungin)

- Perform targeted physical examination (including vital signs) every 3 days (Note: Subjects receiving treatment in the outpatient setting may have less frequent assessments, but not less than at least once every 7 days. Close monitoring of subjects treated in the outpatient setting is required);

- CBC with differential every seven days (same as in screening);
- Serum chemistry every seven days (same as in screening).

6.3. End of IV Anidulafungin Therapy

The following assessments will be performed on the last day (or within 24 hours of the last day) of IV anidulafungin treatment:

- Targeted physical examination (including vital signs);
- Assess signs and symptoms of *Candida* infection;
- Fundoscopic examination, only if the baseline fundoscopic examination was abnormal;
- Blood cultures (for subjects with microbiologically confirmed ICC);
- Specimen culture (from other normally sterile sites as clinically indicated);
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);
- Echocardiogram, either transesophageal (preferred) or transthoracic (to be performed only in subjects with *Candida* endocarditis) **(not applicable to Korean and Portuguese investigator sites)**;
- ** Please Note ** To be performed at the End of Treatment with IV anidulafungin in subjects who are not switched to oral fluconazole. In subjects who are switched to oral fluconazole, echocardiogram should be deferred to the End of Oral Therapy visit.
- Magnetic Resonance Imaging (MRI) study (to be performed only in subjects with *Candida* osteomyelitis) **(not applicable to Korean and Portuguese investigator sites)**;
- ** Please Note ** To be performed at the End of Treatment with IV anidulafungin in subjects who are not switched to oral fluconazole. In subjects who are switched to oral fluconazole, echocardiogram should be deferred to the End of Oral Therapy visit.
- Evaluation of clinical and microbiologic response (See [Section 7.4](#)) (to be performed only in subjects with microbiologically confirmed ICC);
- Urine or serum pregnancy test (for females of childbearing potential) to be done at the End of Treatment period in subjects who are not switched to oral therapy.
- Record adverse events and concomitant medications.

6.4. End of Oral Therapy (if applicable)

The following assessments will be performed on the last day (or within 24 hours of the last day) of oral anidulafungin treatment:

- Targeted physical examination (including vital signs);
- Assess signs and symptoms of *Candida* infection;
- Fundoscopic examination, only if the baseline fundoscopic examination was abnormal;
- Blood cultures (for subjects with microbiologically confirmed ICC);
- Specimen culture (from other normally sterile sites as clinically indicated);
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);
- Echocardiogram, either transesophageal (preferred) or transthoracic (to be performed only in subjects with *Candida* endocarditis) **(not applicable to Korean and Portuguese investigator sites)**;
- Magnetic Resonance Imaging (MRI) study (to be performed only in subjects with *Candida* osteomyelitis) **(not applicable to Korean and Portuguese investigator sites)**;
- Urine or serum pregnancy test (for females of childbearing potential);
- Evaluation of clinical and microbiologic response (See [Section 7.4](#)) (to be performed only in subjects with microbiologically confirmed ICC).
- Record adverse events and concomitant medications.

**** Please Note **** The EOT is defined as either (1) the end of IV anidulafungin if subject is not switched to oral fluconazole, or (2) the end of the oral fluconazole if subject is switched from IV anidulafungin to oral fluconazole.

6.5. Follow Up Visit (End of Treatment + 2 weeks)

The following assessment will be performed 2-weeks (or within 2 days of the scheduled 2-week follow-up visit) after the last dose of study drug treatment. *This visit is only required in subjects with microbiologically confirmed invasive candidiasis/candidemia (ICC):*

- Targeted physical examination (including vital signs);
- Temperature;

- Assess signs and symptoms of *Candida* infection;
- Fundoscopic examination, only if the baseline fundoscopic examination was abnormal;
- Blood cultures (only if clinically indicated);
- Specimen culture (from other normally sterile sites, only if clinically indicated);
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);
- Evaluation of clinical and microbiologic response (See [Section 7.4](#)) (to be performed only in subjects with microbiologically confirmed ICC);
- Record adverse events.
- Record the use of systemic antifungal medications since the last study visit; if the subject experienced an adverse event, record all concomitant medications the subject was receiving at the time of the adverse event.

6.6. Long Term Follow-Up (End of Treatment + 6 weeks)

The following assessments will be performed 6-weeks (or within 1 week of the scheduled 6-week follow-up visit) after the last dose of study drug treatment:

- Targeted physical examination (including vital signs);
- Temperature;
- Assess signs and symptoms of *Candida* infection;
- Fundoscopic examination, only if the baseline fundoscopic examination was abnormal;
- Blood cultures (only if clinically indicated);
- Specimen culture (from other normally sterile sites as clinically indicated);
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);
- Urine or serum pregnancy test (for females of childbearing potential).

- Evaluation of clinical and microbiologic response (See [Section 7.4](#)) (to be performed only in subjects with microbiologically confirmed ICC);
- Record adverse events.
- Record the use of systemic antifungal medications since the last study visit; if the subject experienced an adverse event, record all concomitant medications the subject was receiving at the time of the adverse event.

6.7. Subject Withdrawal

Subjects may withdraw from the study treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral reasons or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site. If a subject is withdrawn from the study treatment, on the last day of study drug administration the investigator will perform all EOT procedures and complete the EOT CRF.

In addition, these subjects will continue to be monitored for the occurrence of adverse effects (serious and non-serious) for up to 6 weeks after the last dose of study treatment. Refer to [Section 6.5](#) and [Section 6.6](#) for follow-up visit requirements.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.8. Subject Withdrawal Due to Lack of Confirmation of *Candida* Infection

Subjects who were enrolled on the basis of suspected *Candida* infection may remain in the study and receive study treatment at the discretion of the investigator, if culture results are either negative for *Candida* sp. or not obtained after treatment initiation. Should the investigator choose to withdraw the subject from study treatment, on the last day of study drug administration the investigator will perform all EOT procedures and complete the EOT CRF. In addition, these subjects will continue to be monitored for the occurrence of adverse effects (serious and non-serious) for up to 6 weeks after the last dose of study treatment. Refer to [Section 6.5](#) and [Section 6.6](#) for follow-up visit requirements.

6.9. Discontinuation Criteria for Abnormal Liver Function Tests

It is important for investigators to monitor carefully for any adverse events, including elevations of liver function tests that could be related to anidulafungin.

Subjects who experience an increase in AST, ALT or total bilirubin that exceeds either one of the two thresholds outlined below, at any time during the study, must be discontinued from treatment with anidulafungin.

- AST and/or ALT >3x the upper limit of normal AND total bilirubin >1.5x the upper limit of normal, and no evidence of biliary obstruction (eg, elevated alkaline phosphatase in the context of gallbladder disease, bile duct disease or malignancy) or other explanation (eg, viral hepatitis, autoimmune hepatitis);
- AST and/or ALT >10x the upper limit of normal, regardless of causality.

Note: These subjects will be discontinued from study treatment but will remain in the study for safety monitoring according to the procedures described in [Section 6.7](#). These subjects are required to return for the 2- and 6-week follow-up visits.

6.10. Discontinuation Criteria for Persistent Candidemia

Subjects who were either candidemic at baseline or become candidemic during the course of the study will be considered treatment failures and discontinued from study treatment if candidemia persists for more than 7 days.

Note: These subjects will be discontinued from study treatment but will remain in the study for safety monitoring according to the procedures described in [Section 6.7](#). These subjects are required to return for the 2- and 6-week follow-up visits.

7. ASSESSMENTS

All subjects will undergo safety, clinical, laboratory and PK assessments during this trial.

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test can not be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Pregnancy Testing

For female subjects of childbearing potential, a urine or serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, end of IV therapy, end of oral therapy, and long term follow up visit. A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or if required by local regulations.

7.2. Clinical Assessments

All clinical assessments are to be performed by the Investigator and recorded in the subject's chart and the Case Report Form (CRF). It will be particularly important for Investigators to carefully monitor subjects for any Adverse Events that could be related to the study drug.

Clinical assessments will include:

- a. Complete physical examination: height, weight, general appearance and vital signs (systolic and diastolic blood pressure, temperature, pulse and respiratory rates); cardiovascular system; abdomen and gastrointestinal system; urinary system; respiratory system; and central nervous system. Other examinations may also be performed at the discretion of the Investigator.
- b. Targeted physical examination: this is a simplified abbreviated and focused physical exam relevant to the patient's condition and progress as determined by the Investigator and includes the vital signs.
- c. Medical History: including (as appropriate) age, gender, medical history, surgical history, prior medications (only antifungal agents within 30 days prior to enrolment), adverse reactions to medications, and history of hepatic, renal, or cardiovascular systems.
- d. Signs and symptoms of *Candida* infection: The signs and symptoms of *Candida* infection are diverse and dependent on disease severity, the site of infection and status of the host immune system. Constitutional symptoms suggestive of systemic infection include fever and sepsis (eg, tachycardia, hypotension). Infection of visceral organ(s) typically manifest as organ dysfunction and may include radiologic findings demonstrative of singular or multiple microabscesses. The most frequently observed signs and symptoms of commonly encountered forms of candidiasis are listed in the Case Report Form. However, the investigator is referred to the most recent clinical practice guidelines (published in March 2009), from the Infectious Diseases Society of America on the management of Candidiasis for comprehensive review of signs and symptoms associated with this disease.⁸

7.3. Global Response Determination

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure at the EOIVT, EOT and FU visits. Rates of relapse (recurrence) and/or new infection will be assessed at the FU visits. These efficacy parameters will be derived in the analysis from the investigator's assessment of clinical and microbiologic response, and are defined below.

Global response, which will be derived from both investigator assessed clinical and microbiologic responses, will be defined as follows:

- **Success:** A subject will be categorized as a success if there is both a clinical success (cure or improvement) and microbiological success (eradication or presumed eradication);

- **Failure**: A subject will be categorized as a failure if there is either a clinical or microbiological failure (excluding clinical and microbiological responses of indeterminate);
- **Indeterminate**: A subject will be categorized as indeterminate if there is a clinical and/or microbiological response of indeterminate and neither response was a failure.

7.4. Clinical and Microbiologic Response Assessment

7.4.1. Subjects with Invasive Candidiasis/Candidemia (Except for Subjects with *Candida* Endocarditis or *Candida* Osteomyelitis)

7.4.1.1. Clinical Response at End of IV Treatment (EOIVT) and End of Treatment (EOT)

Clinical response is defined as follows:

- **Cure**: Resolution of signs and symptoms attributed to *Candida* infection; no additional systemic antifungal;
- **Improvement**: Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal;
- **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 a clinical efficacy response of indeterminate.

7.4.1.2. Microbiologic Response at End of IV Treatment (EOIVT) and End of Treatment (EOT)

Microbiologic response is defined as follows:

- **Eradication or presumed eradication**: Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful outcome.
- **Persistence (documented or presumed)**: Any baseline *Candida* spp. 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.

7.4.1.3. Clinical Response at the 2-Week and 6-Week Follow-Up Visits

Clinical response is defined as follows:

- **Cure**: Resolution of signs and symptoms attributed to *Candida* infection; no additional systemic antifungal;
- **Improvement**: Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal;
- **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 a clinical efficacy response of indeterminate.

7.4.1.4. Microbiologic Response at the 2-Week and 6-Week Follow-Up Visits

Microbiologic response is defined as follows:

- **Eradication or presumed eradication**: Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful outcome;
- **Persistence (documented or presumed)**: Any baseline *Candida* spp. 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* spp 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;
- **New Infection**: Subject presenting with clinical failure with the emergence of new *Candida* spp at the original site of infection or at a distant site of infection.

7.4.2. Subjects with Candida Endocarditis and Candida Osteomyelitis Only (This section is not applicable to Korean and Portuguese investigator sites.)

7.4.2.1. Clinical Reponse at End of IV Treatment (EOIVT) and End of Treatment (EOT)

Clinical response is defined as follows:

- **Cure**: Resolution of signs and symptoms attributed to *Candida* infection; no additional/ongoing systemic antifungal therapy;

- **Improvement:** Significant, but incomplete resolution of signs and symptoms of the *Candida* infection;
- **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 a clinical efficacy response of indeterminate.

7.4.2.2. Microbiologic Response at End of IV Treatment (EOIVT) and End of Treatment (EOT)

Microbiologic response is defined as follows:

- **Eradication or presumed eradication:** Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful outcome;
- **Persistence (documented or presumed):** Any baseline *Candida* spp. 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.

7.4.2.3. Clinical Response at the 2-Week and 6-Week Follow-Up Visits

Clinical response is defined as follows:

- **Cure:** Resolution of signs and symptoms attributed to *Candida* infection; no additional/ongoing systemic antifungal;
- **Improvement:** Significant, but incomplete resolution of signs and symptoms of the *Candida* infection;
- **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 a clinical efficacy response of indeterminate.

7.4.2.4. Micro Response at the 2-Week and 6-Week Follow-Up Visits

Microbiologic response is defined as follows:

- **Eradication or presumed eradication:** Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful outcome;
- **Persistence (documented or presumed):** Any baseline *Candida* spp. 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* spp 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;
- **New Infection:** Subject presenting with clinical failure with the emergence of new *Candida* spp at the original site of infection or at a distant site of infection.

In addition, subjects will be contacted (eg, in person, by telephone, mail, or e-mail) to determine survival status at 2-Week and 6-Week after EOT. If a subject cannot be contacted, survival status may be obtained through a family member, hospital/clinic records or information that is in the public domain.

7.5. Electrocardiogram (ECG)

After the initiation of the first dose of anidulafungin, if a ventricular arrhythmia occurs and is assessed by the investigator as clinically significant, the investigator should collect a standard 12-lead electrocardiogram (ECG) at that time.

The investigator or a designated person will determine the appropriateness of the ECG recordings for interpretation. It may be necessary to repeat the ECG to obtain a readable tracing, calibrate the machine, or rule out improper lead placement. A printout of the ECG will be sent out to a central laboratory.

7.6. Fundoscopic Examinations

Fundoscopy exams should be performed with pupils dilated if possible. In addition, when required by the protocol, the exam should be performed by an ophthalmologist unless it is not possible for practical reasons, in which case it may be performed by the Principal investigator or subinvestigator(s).

If it is not possible to perform a fundoscopic examination prior to the first dose of study drug, it may be performed up to 48 hours after the first dose. Under extenuating circumstances, if a fundoscopic examination cannot be performed prior to the first dose or within 48 hours, every effort should be made to perform the examination as soon as possible thereafter.

**** Please Note **** If the baseline fundoscopic examination is positive for findings consistent with *Candida* endophthalmitis, then a repeat fundoscopic examination is required at the end of treatment and at the 2- and 6-week follow-up visits. Additional fundoscopic assessments, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional fundoscopic examinations are performed, the results should be recorded on the case report form.

7.7. Safety Assessments

All subjects who receive at least one dose of study medication will be evaluated for safety. Safety will be assessed at each visit through physical examination, assessment of laboratory parameters and assessment of adverse events. It will be particularly important for investigators to carefully monitor subjects for any adverse events, including elevations in liver function tests, that could be related to anidulafungin.

7.8. Laboratory Assessments

7.8.1. Hematology and Blood Chemistry

The study sites will process routine hematology and blood chemistry specimens locally.

- CBC with differential (Hematology panel) will include: red blood cell count, reticulocytes (absolute or percent), white blood cell count, neutrophils (absolute or percent), lymphocytes (absolute or percent), monocytes (absolute or percent), basophils (absolute or percent) and platelets;
- Serum Chemistry will include: sodium, potassium, chloride, bicarbonate, BUN (or urea), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, albumin, glucose, calcium, magnesium.

7.8.2. Echocardiogram (For Subjects with *Candida* Endocarditis) (This section is not applicable to Korean and Portuguese investigator sites.)

For subjects with *Candida* endocarditis, either a transesophageal (preferred) or transthoracic echocardiogram will be performed at the time of screening. If, however, the test was already performed within the previous 96 hours (of the screening visit), then an echocardiogram at the time of screening is not required. In this case, results of the echocardiogram used to support the initial diagnosis will be recorded in the case report form.

An echocardiogram will also be performed at the end of study treatment (ie, at the end of treatment with IV anidulafungin, or at the end of treatment with oral fluconazole in subjects who are switched to oral therapy). Results of the echocardiogram will be recorded on the appropriate case report form.

Additional echocardiogram assessments, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional echocardiogram assessments are performed, the results should be recorded on the case report form.

**** Important Note **** In subjects with *Candida* endocarditis 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.

7.8.3. Magnetic Resonance Imaging (MRI) Studies (For Subjects with *Candida* Osteomyelitis) (This section is not applicable to Korean and Portuguese investigator sites.)

For subjects with *Candida* osteomyelitis, a magnetic resonance imaging (MRI) study will be performed at the time of screening. If, however, the test was already performed within the previous 96 hours (of the screening visit), then an MRI at the time of screening is not required. In this case, results of the MRI used to support the initial diagnosis will be recorded in the case report form.

A magnetic resonance imaging (MRI) study of the affected area will also be performed at the end of study treatment (ie, at the end of treatment with IV anidulafungin, or at the end of treatment with oral fluconazole in subjects who are switched to oral therapy). Results of the MRI study will be recorded on the appropriate case report form.

Additional MRI studies, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional MRI studies are performed, the results should be recorded on the case report form.

**** Important Note **** In subjects with *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.

7.8.4. Mycologic Testing for *Candida* Infection

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

7.8.5. Microbiological Determinations

1. **Screening Culture(s):** The ‘screening visit culture’ is the culture result that qualifies the subject with definitive diagnosis of ICC for study entry (along with other inclusion criteria) and is from a blood or tissue sample (obtained from a normally sterile) that was obtained within 96 hours prior to the screening visit, that is positive for *Candida* sp. The result of this culture will be recorded on the ‘screening visit’ case report form.

In the event the subject is enrolled on the basis of mycologic evidence suggestive of *Candida* infection (see [Section 4.1](#), Inclusion Criteria) and the organism has not yet been identified, once the final identification has been determined the result will be recorded on the ‘screening visit’ case report form.

2. **On-Study Blood Cultures:** Blood cultures will be obtained on Day 1 (prior to the administration of the first dose) in all subjects.
 - a. If a positive culture is returned, repeat cultures are required at least every 3 days until 2 consecutive cultures, separated by at least 24 hours, are confirmed to be negative while on study medication. Blood cultures will be obtained at the end of IV therapy (EOIVT), and at the end of oral therapy (in subjects switched to oral fluconazole). For subjects who are prematurely discontinued from treatment for any reason, a blood sample for culture should be obtained only if it is clinically indicated. A blood culture at the 2-week and 6-week follow-up visit is required only if clinically indicated.
 - b. For subjects *without microbiologically confirmed ICC*, further cultures will be obtained at the discretion of the investigator. The results of the cultures should be recorded on the case report form.
 - c. Additional cultures beyond those required by the protocol may be obtained at any time at the investigator’s discretion, as clinically indicated. The results of the cultures should be recorded on the case report form.
3. **Tissue Cultures:** For subjects *with microbiologically confirmed ICC* whose screening cultures were obtained from sterile site samples (other than blood), follow-up cultures from the same anatomical site should be repeated only as clinically indicated, otherwise they are not required. For subjects *without microbiologically confirmed ICC*, cultures will be obtained as clinically indicated at the discretion of the investigator. The results of the cultures should be recorded on the case report form.

Investigators will send specimens (blood or other) to their local certified laboratory for culture (incubation should be a minimum of five days if not positive before then). Each laboratory will follow its usual procedures for identification of the species and susceptibility testing to marketed agents.

Additionally, all *Candida* isolates must be preserved for shipment to the reference laboratory to confirm identification and perform susceptibility testing. This includes the original isolate that the diagnosis for inclusion into the study was made, as well as all subsequently recovered *Candida* isolates from any sterile site. If more than one species of *Candida* is isolated from a single culture, all isolates must be sent to the reference laboratory. The susceptibility testing will be conducted using the current Clinical and Laboratory Standards Institute (CLSI) approved standard method.

7.9. Pharmacokinetic Assessments

7.9.1. Blood Sampling for Subjects in the PK Sub-Study (1 Month to <2 Years of Age)

The first 6 children aged <2 years enrolled in the PK substudy (at selected centers) will undergo the PK sampling as described below.

Prior to the administration of the first dose of study drug, a plasma sample (0.1 – 0.2 mL) should be obtained and sent to the reference laboratory to test for assay interference. Excess blood collected for safety laboratory testing may be used for this sample, otherwise it should be collected directly from the subject.

Following initiation of treatment, blood samples (approximately 0.3 - 0.5 mL each) will be collected for anidulafungin measurement at the following 6 time points.

- On Day 1 (receiving 3 mg/kg IV infusion): 2 minutes before the end of infusion;
- **On Day 2 (receiving 1.5 mg/kg IV infusion):** Just prior to the start of infusion; 2 minutes before the end of infusion, 6, 12 and 24 hours after the start of infusion.

Due to the special conditions of the study population, the sampling time and day can be flexible in order to fit the subject's schedule. For instance, if serial pharmacokinetic sampling cannot be scheduled on Day 2, subjects will continue to remain on IV treatment to allow sample collection at a later date. The actual sampling time and date will be recorded in the CRF.

7.9.2. Blood Sampling for All Subjects (Except for the First Six Subjects Age 1 Month to <2 Yrs Enrolled in the PK Sub-Study)

Two aliquots of blood samples (one: approximately 0.3 - 0.5 mL for anidulafungin measurement; the other: approximately 1 mL for polysorbate 80 [a formulation excipient] measurement) will be collected at 3 - 5 of the following occasions during the study for all subjects (except for the first 6 subjects enrolled in the 1 month - <2 year age group):

- **Day 1:** Post-dose (between 0-2 hours following the end of anidulafungin infusion);
- **Day 3:** Pre-dose (just prior to the start of anidulafungin infusion);
- **Day 5:** Post-dose (between 0-3 hours following the end of anidulafungin infusion);

- **Day 7:** Delayed post-dose (between 6-12 hours following the end of anidulafungin infusion);
- **Day 9:** Pre-dose (just prior to the start of anidulafungin infusion).

The above sampling days are flexible and could be modified at the discretion of each study center as long as samples are collected during the treatment period with anidulafungin. If only 3 samples can be collected, preference is for the two post-dose and one delayed post-dose time points. The delayed post-dose sample may be collected prior to Day 7, for example on Day 3, to facilitate the preferred sample collection.

Blood samples for anidulafungin and polysorbate 80 measurements will be centrifuged at approximately 1700 g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C within 1 hour of for anidulafungin and at approximately -70°C within 30 minutes of collection for polysorbate 80. Detailed information on sample collection and/or processing information for anidulafungin and polysorbate 80 measurements will be provided in the central laboratory manual.

Plasma samples will be analyzed for anidulafungin and polysorbate 80 using validated analytical methods in compliance with Pfizer standard operation procedures.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

8.2. Reporting Period

For serious adverse events, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including the 6 week follow-up visit.

SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

- Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit.
- Reported SAEs occurring after the active report period will be reported in the safety database but will not be recorded in the CRF (ie, clinical database).

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;

- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breast feeding;
- Medication error;
- Occupational exposure

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life function);
- Results in congenital anomaly/birth defect;

- Lack of efficacy in an approved indication should be reported as a serious adverse event;
- Lack of efficacy should be reported as an adverse event when it is associated with a serious adverse event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other adverse event outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.5.1. Protocol-Specified Serious Adverse Events

The following expected, SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see [Section 8.13.1 SAE Reporting Requirements](#)) but will not be reported individually in an expedited manner because they are anticipated to occur in the study population:

- Progression of underlying malignancy (eg, leukemia, lymphoma);
- Aspergillosis;
- Bacterial infection.

Should an aggregate analysis indicate that these prespecified events occur more frequently than expected based on the expectation of frequency of the event(s) in question in the population for comparison, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analysis of safety data will be performed on a regular basis per internal standard operating procedures.

8.5.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥ 3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥ 2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤ 2 X ULN or not available.
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
 - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥ 2 times the baseline values and ≥ 3 X ULN, or ≥ 8 X ULN (whichever is smaller).
- **Concurrent with**
 - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal **or** ≥ 3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as serious adverse events.

8.6. Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.7. Severity Assessment

If required on the adverse event case report forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (See Section on [Reporting Requirements](#)). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a serious adverse event is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.9. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, due to treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source

documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.10. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.11. Withdrawal Due to Adverse Events (See Also Section on [Subject Withdrawal](#))

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a subject withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about adverse events.

8.13. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.13.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. The information collected for serious adverse events is more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.13.2. Non-Serious Adverse Event Reporting Requirements

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

8.13.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse events reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan, which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Analysis of Primary Endpoint

The primary analysis will be the evaluation of adverse events throughout the trial, laboratory tests, and physical examination.

The set of subjects for this evaluation will be the Safety population, defined as all subjects with at least 1 dose of study medication.

The following parameters will be summarized: rates of discontinuation, adverse events, ECG findings (if applicable), and laboratory abnormalities.

The Sponsor has standard algorithms for reporting adverse events and clinical laboratory test results, and these will be employed in the analysis of the data from this trial. Safety data will be subject to clinical review and summarized by appropriate descriptive statistics. Descriptive statistics for categorical data will include frequencies and/or percentages.

9.2. Analysis of Secondary Endpoints

The efficacy analysis will be an assessment of global response at EOIVT, EOT, 2 week and 6 week FU visits. Global response will be derived from the investigator's assessment of clinical and microbiological response as defined in [Section 7.4](#). The analysis will be conducted by frequencies and percentages of global response by determination (success, failure). These efficacy analyses will be assessed in the Modified Intent-to-Treat (MITT) population, which will be defined as all subjects who have received at least one dose of study drug and who have microbiological confirmation of *Candida* infection.

Rates of relapse (recurrence) and new infection at FU visits will also be derived from the investigator's assessment of clinical and microbiologic response as defined in [Section 7.4](#), and analyzed. Time to death will be analyzed and all-cause mortality rates determined.

9.3. Pharmacokinetic Analyses

9.3.1. Non-compartmental Pharmacokinetic Analysis

Non-compartmental pharmacokinetic analysis will be performed on individual plasma anidulafungin concentration-time data from children <2 years to obtain the following pharmacokinetic parameters of anidulafungin: AUC₂₄ and C_{max}. Data listings and summary statistics will be generated for each pharmacokinetic parameter and presented in graphical and/or tabular format.

9.3.2. Population Pharmacokinetic-Pharmacodynamic (PK-PD) Analysis

Measures of efficacy or safety versus steady-state anidulafungin exposure (AUC₂₄) will be modeled using a nonlinear mixed effects approach as appropriate.

Firstly, population pharmacokinetic analysis on the plasma concentration data of anidulafungin will be performed to derive the conditional estimation of individual AUC₂₄.

Population PK-PD models will be developed using an iterative process, adapting the model to improve the goodness of fit. In the case that only one record on the PD data (efficacy or safety endpoints) will be obtained from each subject, a Naïve Pooled Data (NPD) analysis will be considered for PK-PD analysis. In the case that multiple measurements are available, the time to event analysis may be explored as appropriate.

If a sufficient number of MIC values are available, the association between the PK-PD index, AUC/MIC, and efficacy will also be evaluated using the same approach. If data permit, the association between C_{max}/MIC and efficacy will be explored.

Polysorbate 80 exposure parameters (eg, AUC₂₄, C_{max}) will also be estimated using a nonlinear mixed effects approach as appropriate.

9.4. Sample Size Determination

Since this is a descriptive study, sample size calculations were not performed. A sample size of 60 evaluable subjects for this study was chosen based on the number of subjects estimated to be necessary to provide adequate information for assessing efficacy, safety and tolerability in children with ICC. Evaluable subjects are those that have received at least one dose of study medication and have a confirmed *Candida* infection.

9.5. Safety Analysis

All subjects who have received at least 1 dose of study medication will be included in the safety analyses. Adverse events and other safety data, including ECG (if applicable) and laboratory data will be reviewed and summarized on an ongoing basis during the study. The Sponsor has standard algorithms for reporting adverse events and clinical laboratory test results, and these will be employed in the analysis of the data from this study. Safety and tolerability data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

9.6. Interim Analysis

Subjects will be stratified by age (1 month - <2 years, 2 - <5 years, and 5 - <18 years), allowing 20 ± 2 subjects in each stratum. An interim analysis to assess safety, PK and efficacy will be conducted when approximately 20 ± 2 subjects for age cohorts 2 to <5 years and 5 to < 18 years have completed the study.

9.7. Data Monitoring Committee

This study will use an Independent Data Monitoring Committee (IDMC).

The IDMC will be responsible for ongoing monitoring of the efficacy and safety of subjects in the study according to the Charter. Any recommendations made by the IDMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate. In this instance, such disease-related efficacy endpoints are not reported individually as SAEs.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and

detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Counsel for International Organization of Medical Science 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by law. When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical

code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent/assent documents used during the informed consent process, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use, and available for inspection.

The investigator must ensure that each study subject, and/or his/her legal representative or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must re-consent as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and assent from each subject (if applicable) before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent/assent document.

12.4. Reporting Of Safety Issues And Serious Breaches Of The Protocol Or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF STUDY

13.1. End of Study in a Member State

End of Study in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Study in All Participating Countries

End of Study in all participating countries is defined as Last Subject Last Visit (LSLV) for the entire study.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems (such as repeated severe or serious AEs warranting temporary or permanent study termination), or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of anidulafungin at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within a reasonable timeframe. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

- Publication of study results is discussed in the Clinical Study Agreement (CSA).

15.1. Communication of Results by Pfizer:

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

Investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Edmond MB et al. Nosocomial bloodstream infections in United States hospitals: a three-year analysis. *Clin Infect Dis* 1999; 29:239-244.
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3. Rodríguez-Núñez A et al. Incidence and mortality of proven invasive *Candida* infections in paediatric intensive care patients. *Infect Control Hosp Epidemiol* 2001; 22:477-8.
4. ERAXIS™ (anidulafungin), United States Package Insert 2007, Pfizer Inc: New York, NY.
5. Anidulafungin Investigator Brochure. June 2010.
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7. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *Paediatrics* 2004; 114: 555-576.
8. Pappas PG, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD. Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009. 48:503-535.

Appendix 1. CLINICAL PROTOCOL AMENDMENT 1

Current Amendment: 1			
Amendment No. Amendment 1	Date 12 March 2008	Country (ies)	Site(s)
Previous Amendments:			
Amendment No.	Date	Country (ies)	Site(s)

SUMMARY

Reason(s) for Amendment

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

- The “change from” section represents the current text in the protocol. Bolded text is used to indicate the addition of information to the current text, and strike-out of text (eg, text) is used to show the deletion of information from the current text.
- The “change to” section represents the revised text, with the revisions shown in the “change from” section in normal text.

Section

Change From

Change To

1. Section Protocol Summary, Paragraph 1, 3

Change From

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

The primary study objective is to assess the safety and tolerability of anidulafungin when used to treat children with ~~candidaemia and/or other forms of invasive candidiasis (ICC)~~. Additional assessments will include global response at the end of IV therapy (EOIVT) and subsequent time points, exposure-response relationship, the rates of relapse and emerging infection at follow up (FU) visits, and **analysis of time to death all-cause mortality at during study therapy and follow-up visits through EOIVT and at the end of treatment (EOT)**.

Change To

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

The primary study objective is to assess the safety and tolerability of anidulafungin when used to treat children with (ICC). Additional assessments will include global response at the End of IV Therapy (EOIVT) and subsequent time points, exposure-response relationship, the rates of relapse and emerging infection at follow up (FU) visits, and analysis of time to death during study therapy and follow-up visits.

2. Section Protocol Summary Background and Rationale, Paragraph 3

Change From

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 candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) **in adults**. To date, there are no clinical studies evaluating anidulafungin in paediatric **patients** with invasive *Candida* infection. This study will assess the pharmacokinetics, safety and efficacy of anidulafungin in **patients** 1 month to <18 years of age with ICC. Exposure-response relationships of anidulafungin will also be assessed in a population pharmacokinetic-pharmacodynamic (PK-PD) analysis.

Change To

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 candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in adults. To date, there are no clinical studies evaluating anidulafungin in paediatric patients with invasive *Candida* infection. This study will assess the

pharmacokinetics, safety and efficacy of anidulafungin in patients 1 month to <18 years of age with ICC. Exposure-response relationships of anidulafungin will also be assessed in a population pharmacokinetic-pharmacodynamic (PK-PD) analysis.

3. Section Protocol Summary Study Design, Paragraphs 2, 4, 5, 6, 7

Change From

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 10 days of IV treatment, provided that the pre-specified criteria are met.

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine pregnancy test (for females of childbearing potential), ~~chest X-ray~~, fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated on Days 3 and 7 and every third day thereafter until two cultures separated by at least 24 hours are confirmed to be negative. **Any negative blood culture after Day 1 (per protocol schedule or otherwise) must be repeated after 24 hours.**

Anidulafungin pharmacokinetics will be assessed in the first 6 subjects aged between 1 month to <2 years, to be enrolled at selected centers. Use of a second systemic antifungal agent (eg, amphotericin B) will be permitted for these 6 subjects only. Three subjects in this cohort will be between 1 and <6 months of age and 3 subjects will be between 6 months and <2 years of age, **which will be enrolled in parallel**. Data from these 6 subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. The exposure data from these subjects will be used to confirm if the recommended dosing regimen is appropriate for subjects aged <2 years. After the PK data is evaluated and dosing regimen is confirmed, subjects between 1 month to <2 years of age will be permitted to be enrolled at all sites. Subsequent to this time point, use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted.

A population PK-PD analysis will also be performed in all other subjects enrolled and will include subjects <2 years of age who are not part of the 6 subject cohort described above, in which 3 to 4 **5** sparse pharmacokinetic samples will be collected.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure at the EOIVT, EOT, 2-week FU and 6-week FU visits. ~~The main efficacy assessment will be determined at EOTEIVT.~~ Rates of relapse 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.

Change To

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 10 days of IV treatment, provided that the pre-specified criteria are met.

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated on Days 3 and 7 and every third day thereafter until two cultures separated by at least 24 hours are confirmed to be negative. Any negative blood culture after Day 1 (per protocol schedule or otherwise) must be repeated after 24 hours.

Anidulafungin pharmacokinetics will be assessed in the first 6 subjects aged between 1 month to <2 years, to be enrolled at selected centers. Use of a second systemic antifungal agent (eg, amphotericin B) will be permitted for these 6 subjects only. Three subjects in this cohort will be between 1 and <6 months of age and 3 subjects will be between 6 months and <2 years of age, which will be enrolled in parallel. Data from these 6 subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. The exposure data from these subjects will be used to confirm if the recommended dosing regimen is appropriate for subjects aged <2 years. After the PK data is evaluated and dosing regimen is confirmed, subjects between 1 month to <2 years of age will be permitted to be enrolled at all sites. Subsequent to this time point, use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted.

A population PK-PD analysis will also be performed in all other subjects enrolled and will include subjects <2 years of age who are not part of the 6 subject cohort described above, in which 3 to 5 sparse pharmacokinetic samples will be collected.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure at the EOIVT, EOT, 2-week FU and 6-week FU visits. Rates of relapse 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.

4. Section Protocol Summary Objectives Secondary, Bullet 6

Change From

- To assess all-cause mortality ~~at the EOIVT and EOT time points~~ **during study therapy and FU visits.**

Change To

- To assess all-cause mortality during study therapy and FU visits.

5. Section Protocol Summary Endpoints, Secondary Endpoints, Bullet 6

Change From

- All-cause mortality **during study therapy and follow-up visits.** ~~at the EOIVT and EOT time points.~~

Change To

- All-cause mortality during study therapy and follow-up visits.

6. Section, Statistical Methods, Paragraphs 1, 2, 3, 4

Change From

The primary analysis will be the evaluation of adverse events throughout the trial, laboratory tests, temperature, and physical examination. The set of subjects for this evaluation will be the Safety population, defined as all subjects with at least 1 dose of study medication. The following parameters will be summarized: rates of discontinuation, adverse events, **and** laboratory abnormalities, ~~changes in temperature, signs and symptoms, and changes in fundoscopic examination (if applicable).~~ Safety data will be descriptively summarized. Descriptive statistics for categorical data will include frequencies and/or percentages.

Secondary efficacy analyses will be assessed in the Modified Intent-to-Treat (MITT) population, defined as all subjects who have received at least one dose of study drug and who have microbiological evidence of *Candida* species infection. The ~~main~~ efficacy analysis will be an assessment of global response, ~~at EOT and EOIVT. The main analysis will be~~ conducted by frequencies and percentages of global response (success, failure).

Supportive analyses of the ~~main~~ efficacy endpoint **of global response at EOT and EOIVT** will be performed in the Intent to Treat (ITT) population, consisting of all randomized subjects.

Other analyses will include ~~rate of global response at the EOIVT EOT and FU visits,~~ rates of relapse and emerging infection at FU visits, and **analysis of time to death all-cause mortality rates during study therapy and FU visits at EOIVT and EOT,** using the similar methods as described above.

Change To

The primary analysis will be the evaluation of adverse events throughout the trial, laboratory tests, temperature, and physical examination. The set of subjects for this evaluation will be the Safety population, defined as all subjects with at least 1 dose of study medication. The

following parameters will be summarized: rates of discontinuation, adverse events, and laboratory abnormalities. Safety data will be descriptively summarized. Descriptive statistics for categorical data will include frequencies and/or percentages.

Secondary efficacy analyses will be assessed in the Modified Intent-to-Treat (MITT) population, defined as all subjects who have received at least one dose of study drug and who have microbiological evidence of *Candida* infection. The efficacy analysis will be an assessment of global response, conducted by frequencies and percentages of global response (success, failure).

Supportive analyses of the efficacy endpoint of global response will be performed in the Intent to Treat (ITT) population, consisting of all randomized subjects.

Other analyses will include rates of relapse and emerging infection at FU visits, and analysis of time to death during study therapy and FU visits

7. Section Schedule of Activities

Change From

Schedule of Activities

	Screening ¹	Day 1 Daily through EOT	Day 3	Day 7	Day 10	Days 11-34	End of IV Therapy	End of Oral Therapy (if applicable)	Follow-U p Visit (EOT + 2 weeks) (± 2 days)	Long term Follow-U p (EOT + 6 weeks)
Informed consent	X	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-
Complete physical examination (including blood	X									
Targeted physical examination		✕	X	X	X	Every 3 days	X	X	X	X
Temperature	X	X							X	X
Signs and symptoms	X				X		X	X	X	X
Chest X-ray	X									
Urine pregnancy	X						X	X		
Fundoscopy exam	X						X ⁴	X ⁴	X ⁴	X ⁴
Blood cultures ⁵	X		X	X	X	X	X	X	X	X
Specimen culture or microscopy ⁶	X	X						X	X	X
CBC with differential ⁷	X		X	X		X	X	X	X ⁸	X ⁸
Serum chemistry ⁷	X		X	X		X	X	X	X ⁸	X ⁸
Pharmacokinetic sampling (first 6 subjects 1 month to 2 months) ^{9,10}		Days 1 and 2								
Pharmacokinetic sampling (all other subjects) ¹¹		Days 1, 3, 5, 7 and 9								

Study medication administration		X								
Adverse events and concomitant medications		X							X	X
Concomitant medications		X								
Evaluation of Global Response							X	X	X	X
Follow up evaluation (relapse, new infection, or continued resolution/improvement)									X	X

1. Screening procedures/assessments are to be completed before the first dose of study medication.
2. May occur within 72 hours before the first dose of study medication.
3. For females of childbearing potential. This urine pregnancy test is to be repeated at the end of therapy, IV or Oral.
4. To be completed only if the baseline fundoscopic examination is positive for endophthalmitis.
5. Screening blood culture is to be obtained within 96 hours before first dose of Study Drug (Day 1). Blood cultures will be repeated on Day 3, 7, and every three days until 2 cultures separated by at least 24 hours are confirmed to be negative while on study medication and as clinically indicated. **Pathogen isolated will be documented.**
6. Cultures of other normally sterile sites as clinically indicated. **Pathogen isolated will be documented.**
7. CBC with differential (including RBC count and platelets count), and serum chemistry tests (AST, ALT, Alk-Phos, total Bilirubin, Albumin, BUN, Cr, Bicarbonate, Glucose, Na, K, Ca, Cl, Mg) are to be repeated on Day 3, 7 and every seven days during treatment phase, and repeated at the follow-up visits if clinically significant abnormalities were present on the last day of study medication.
8. Hematology and chemistry tests should be repeated at the follow-up visits if clinically significant abnormalities were present on the last day of study medication.
9. ~~Five~~ **Six** blood samples (0.3 - 0.5 mL each) will be collected for anidulafungin measurement at the following time points in the first 6 subjects: **on Day 1 (receiving 3.0 mg/kg IV infusion): 2 minutes before the end of infusion);** on Day 2 (receiving 1.5 mg/kg IV infusion ~~over 1.5 hours~~); just prior to the start of infusion, ~~88 minutes (equivalent to 2 minutes before the end of infusion)~~, and 6, 12 and 24 hours after the start of infusion. Exact sampling times may be modified to accommodate subject schedules provided that the actual time of collection is documented in the case report form (CRF).
10. For the first 6 subjects aged 1 month to <2 years, use of a second systemic antifungal agent (eg, amphotericin B) will be permitted (these subjects will be enrolled at selected centers).
11. Samples (0.3 - 0.5 mL each) will be collected for anidulafungin measurement at 3-~~45~~ of the following occasions during the study: **Day 1: Post-dose (between 0-2 hours following the end of anidulafungin infusion);** Day 3: Pre-dose (just prior to the start of anidulafungin infusion); Day 5: Post-dose (between 0-3 hours following the end of anidulafungin infusion); Day 7: Delayed

post-dose (between 6-12 hours following the end of anidulafungin infusion); Day 9: Pre-dose (just prior to the start of anidulafungin infusion). Exact sampling times may be modified to accommodate subject schedules as long as the samples are collected during the IV treatment period.

Change To

Schedule of Activities

	Screening ¹	Daily through EOT	Day 3	Day 7	Day 10	Days 11-34	End of IV Therapy	End of Oral Therapy (if applicable)	Follow-Up Visit (EOT + 2 weeks) (± 2 days)	Long term Follow-Up (EOT + 6 weeks) (± 1 week)
Informed consent	X	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-
Complete physical examination (including vital signs) ²	X									
Targeted physical examination			X	X	X	Every 3 days	X	X	X	X
Temperature	X	X							X	X
Signs and symptoms	X				X		X	X	X	X
Urine pregnancy test ³	X						X	X		
Fundoscopy exam	X						X ⁴	X ⁴	X ⁴	X ⁴
Blood cultures ⁵	X		X	X	X	X	X	X	X	X
Specimen culture ⁶	X	X						X	X	X
CBC with differential ⁷	X		X	X		X	X	X	X ⁸	X ⁸
Serum chemistry ⁷	X		X	X		X	X	X	X ⁸	X ⁸
Pharmacokinetic sampling (first 6 subjects 1 month to <2 yrs old) ^{9,10}		Days 1 and 2								
Pharmacokinetic sampling (all other subjects) ¹¹		Days 1, 3, 5, 7 and 9								
Study medication administration		X								

Adverse events		X							X	X
Concomitant medications		X								
Evaluation of Global Response							X	X	X	X
Follow up evaluation (relapse, new infection, or continued resolution/improvement)									X	X

12. Screening procedures/assessments are to be completed before the first dose of study medication.
13. May occur within 72 hours before the first dose of study medication.
14. For females of childbearing potential. This urine pregnancy test is to be repeated at the end of therapy, IV or Oral.
15. To be completed only if the baseline fundoscopic examination is positive for endophthalmitis.
16. Screening blood culture is to be obtained within 96 hours before first dose of Study Drug (Day 1). Blood cultures will be repeated on Day 3, 7, and every three days until 2 cultures separated by at least 24 hours are confirmed to be negative while on study medication and as clinically indicated. Pathogen isolated will be documented.
17. Cultures of other normally sterile sites as clinically indicated. Pathogen isolated will be documented.
18. CBC with differential (including RBC count and platelets count), and serum chemistry tests (AST, ALT, Alk-Phos, total Bilirubin, Albumin, BUN, Cr, Bicarbonate, Glucose, Na, K, Ca, Cl, Mg) are to be repeated on Day 3, 7 and every seven days during treatment phase, and repeated at the follow-up visits if clinically significant abnormalities were present on the last day of study medication.
19. Hematology and chemistry tests should be repeated at the follow-up visits if clinically significant abnormalities were present on the last day of study medication.
20. Six blood samples (0.3 - 0.5 mL each) will be collected for anidulafungin measurement at the following time points in the first 6 subjects: on Day 1 (receiving 3.0 mg/kg IV infusion): 2 minutes before the end of infusion); on Day 2 (receiving 1.5 mg/kg IV infusion): just prior to the start of infusion, 2 minutes before the end of infusion, and 6, 12 and 24 hours after the start of infusion. Exact sampling times may be modified to accommodate subject schedules provided that the actual time of collection is documented in the case report form (CRF).
21. For the first 6 subjects aged 1 month to <2 years, use of a second systemic antifungal agent (eg, amphotericin B) will be permitted (these subjects will be enrolled at selected centers).
22. Samples (0.3 - 0.5 mL each) will be collected for anidulafungin measurement at 3-5 of the following occasions during the study: Day 1: Post-dose (between 0-2 hours following the end of anidulafungin infusion); Day 3: Pre-dose (just prior to the start of anidulafungin infusion); Day 5: Post-dose (between 0-3 hours following the end of anidulafungin infusion); Day 7: Delayed post-dose (between 6-12 hours following the end of anidulafungin infusion); Day 9: Pre-dose (just prior to the start of anidulafungin infusion). Exact sampling times may be modified to accommodate subject schedules as long as the samples are collected during the IV treatment period.

8. Section 1.3.2 Clinical Data, Clinical Pharmacology, Paragraph 3

Change From

In the paediatric population, pharmacokinetic profiles were assessed in a Phase 1/2 multicenter, open-label, sequential dose-escalation study (from 0.75 mg/kg/day to 1.5 mg/kg/day) of IV anidulafungin administered as early empirical therapy to 24 immunocompromised children ages 2 to 17 years with neutropenia. Children were stratified by age, from 2 to 11 years and from 12 to 17 years. There was no relationship between subject age and the peak concentration (C_{max}), area under curve **over dosing interval** (AUC_{24}), weight-normalized clearance (CL), or weight-normalized steady-state volume of distribution (V_{ss}). The pharmacokinetic profiles on a weight-adjusted basis of 0.75 and 1.5 mg/kg/day were similar to the profiles of anidulafungin administered to adults at dosages of 50 and 100 mg/day, respectively.

Change To

In the paediatric population, pharmacokinetic profiles were assessed in a Phase 1/2 multicenter, open-label, sequential dose-escalation study (from 0.75 mg/kg/day to 1.5 mg/kg/day) of IV anidulafungin administered as early empirical therapy to 24 immunocompromised children ages 2 to 17 years with neutropenia. Children were stratified by age, from 2 to 11 years and from 12 to 17 years. There was no relationship between subject age and the peak concentration (C_{max}), area under curve over dosing interval (AUC_{24}), weight-normalized clearance (CL), or weight-normalized steady-state volume of distribution (V_{ss}). The pharmacokinetic profiles on a weight-adjusted basis of 0.75 and 1.5 mg/kg/day were similar to the profiles of anidulafungin administered to adults at dosages of 50 and 100 mg/day, respectively.

9. Section 2.1 Objectives, Secondary, Bullets 2,6

Change From

- To explore pharmacokinetic parameters of anidulafungin in children aged 1 month to <2 years following IV infusion of anidulafungin (~~area under curve over dosing interval~~ (AUC_{24}) and C_{max});
- To assess all-cause mortality **during study therapy and follow-up visits**.~~at the EOIVT and EOT time points.~~

Change To

- To explore pharmacokinetic parameters of anidulafungin in children aged 1 month to <2 years following IV infusion of anidulafungin (AUC_{24} and C_{max});
- To assess all-cause mortality during study therapy and follow-up visits.

10. Section 2.2 Endpoints, Secondary Endpoints. Bullet 6

Change From

All-cause mortality **during study therapy and follow-up visits** ~~at the EOIVT and EOT time points.~~

Change To

All-cause mortality during study therapy and follow-up visits.

11. Section 3, Study Design, Paragraph 5,8

Change From

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine pregnancy test (for females of childbearing potential), ~~chest X-ray~~, fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated on Days 3 and 7 and every third day thereafter until two cultures separated by at least 24 hours are confirmed to be negative. **If blood cultures are performed more frequently than required by the protocol; a second blood culture after 24 hours of any negative culture is required.**

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure at the EOIVT, EOT, 2-week FU and 6-week FU visits. ~~The main efficacy assessment will be determined at EOT.~~ Rates of relapse 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.

Change To

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated on Days 3 and 7 and every third day thereafter until two cultures separated by at least 24 hours are confirmed to be negative. **If blood cultures are performed more frequently than required by the protocol; a second blood culture after 24 hours of any negative culture is required.**

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure at the EOIVT, EOT, 2-week FU and 6-week FU visits. Rates of relapse 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.

12. Section 4.2, Exclusion Criteria, Number 1

Change From

Addition

1. Premature neonates born at gestation of less than 36 weeks (unless the sum of gestational age plus chronological age is at least 44 weeks);

Note: Rounding to the closest week is round up one week if birth occurred on days 4 to 6 of the week and round down one week if birth occurred on days 1 to 3 of the week.

Change To

1. Premature neonates born at gestation of less than 36 weeks (unless the sum of gestational age plus chronological age is at least 44 weeks);

Note: Rounding to the closest week is round up one week if birth occurred on days 4 to 6 of the week and round down one week if birth occurred on days 1 to 3 of the week.

13. Section 4.5, Central Venous Catheter Management, Paragraph 1

Change From

Addition

4.5. Central Venous Catheter Management

Because *Candida* species adhere avidly to materials used in vascular catheters, catheter removal is strongly recommended in the management of candidemia. The date the suspected infected intravascular catheter was inserted and removed will be recorded in the case report form (CRF). The insertion of any new intravascular catheters, including changing catheters over a guide-wire will also be documented on the non-pharmacological treatment procedure record. Any cultures that were done on the tip of the catheter or site of the catheter insertion will be recorded in the CRF.

14. Section 5.1, Allocation to Treatment, Bullet 4

Change From

- Documentation of a negative culture for *Candida* spp from any other sites of infection if identified at enrollment;

Change To

- Documentation of a negative culture for *Candida* spp from any other sites of infection if identified at enrollment;

15. Section 5.2.3, Administration, Paragraph 1

Change From

Anidulafungin will be administered intravenously at an infusion rate not exceeding 1.1 mg/minute. Anidulafungin loading dose of 3.0 mg/kg (not to exceed 200 mg) on the first day of treatment should be administered intravenously over **no more than** 180 minutes. Anidulafungin maintenance dose of 1.5 mg/kg/day (not to exceed 100 mg) on subsequent days should be administered intravenously over **no more than** 90 minutes.

Change To

Anidulafungin will be administered intravenously at an infusion rate not exceeding 1.1 mg/minute. Anidulafungin loading dose of 3.0 mg/kg (not to exceed 200 mg) on the first day of treatment should be administered intravenously over no more than 180 minutes. Anidulafungin maintenance dose of 1.5 mg/kg/day (not to exceed 100 mg) on subsequent days should be administered intravenously over no more than 90 minutes.

16. Section 5.4, Concomitant Medication(s), Paragraph 1

Change From

Any medication that the subject takes other than the study drug specified in the protocol is considered concomitant medication. Information about concomitant medications will be recorded in the case report form (CRF) from the screening visit through the **EOT last follow up visit (EOT + 6 weeks)**. ~~In addition, any antifungal treatments used between EOT and 6-week FU visit will be documented.~~

Change To

Any medication that the subject takes other than the study drug specified in the protocol is considered concomitant medication. Information about concomitant medications will be recorded in the case report form (CRF) from the screening visit through the EOT. In addition, any antifungal treatments used between EOT and 6-week FU visit will be documented.

17. Section 6.1 Screening Visit

Change From

The following screening activities should occur following the informed consent and within two days of the first dose.

- Obtain informed consent/assent (Note: no study procedures may be performed prior to obtaining written informed consent);
- Medical history;
- Complete physical examination (**including blood pressure measurement** vital signs);
- Temperature;
- Assessment of signs and symptoms of Candida infection;
- Chest X-ray;
- Urine ~~or serum~~ pregnancy test (for females of childbearing potential);
- Fundoscopic examination;
- Blood cultures (to be obtained within 96 hours before first dose of Study Drug: Day 1);
- Specimen culture **or microscopy** (from other normally sterile sites as clinically indicated);
- CBC with differential (Complete blood count with differential and RBC count with reticulocyte count and platelets count);
- Serum chemistry [Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline-Phosphatase (Alk-Phos), Total Bilirubin, Albumin, Bicarbonate, Glucose, Urea nitrogen (BUN), Creatinine (Cr), Sodium (Na), Potassium (K), Calcium (Ca), Chloride (Cl), and Magnesium (Mg)].

It is noted that that it may be possible for the screening activities AND Day 1 (first day of study administration) to be the same day. This will be permitted in this protocol.

Change To

The following screening activities should occur following the informed consent and within two days of the first dose.

- Obtain informed consent/assent (Note: no study procedures may be performed prior to obtaining written informed consent);
- Medical history;
- Complete physical examination (including vital signs);

- Temperature;
- Assessment of signs and symptoms of Candida infection;
- Urine pregnancy test (for females of childbearing potential);
- Fundoscopic examination;
- Blood cultures (to be obtained within 96 hours before first dose of Study Drug: Day 1);
- Specimen culture (from other normally sterile sites as clinically indicated);
- CBC with differential (Complete blood count with differential and RBC count with reticulocyte count and platelets count);
- Serum chemistry [Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline-Phosphatase (Alk-Phos), Total Bilirubin, Albumin, Bicarbonate, Glucose, Urea nitrogen (BUN), Creatinine (Cr), Sodium (Na), Potassium (K), Calcium (Ca), Chloride (Cl), and Magnesium (Mg)].

It is noted that that it may be possible for the screening activities AND Day 1 (first day of study administration) to be the same day. This will be permitted in this protocol.

18. Section, 6.2.1 Daily, through end of treatment

Change From

6.2.1 Day 1

~~It is noted that that it may be possible for the screening activities AND Day 1 (first day of study administration) to be the same day. This will be permitted in this protocol.~~

- Study drug administration of loading dose of 3.0 mg/kg (not to exceed 200 mg);
- Study drug administration: **a loading dose of 3.0 mg/kg (not to exceed 200 mg) on Day 1, and of a maintenance dose of 1.5 mg/kg (not to exceed 100 mg) subsequently** Note: ~~A loading dose of 3.0 mg/kg (not to exceed 200 mg) will be administered on the first day of dosing;~~
- Targeted physical examination;
- Temperature;
- Record Adverse Events and Concomitant Medications;

- Cultures of other normally sterile sites as clinically indicated.

Change To

- Study drug administration: a loading dose of 3.0 mg/kg (not to exceed 200 mg) on Day 1, and a maintenance dose of 1.5 mg/kg (not to exceed 100 mg) subsequently;
- Temperature;
- Record Adverse Events and Concomitant Medications;
- Cultures of other normally sterile sites as clinically indicated.

19. Section 6.2.2, Days 1 and 2 ONLY for Sub-study Subjects (first 6 subjects aged 1 month to <2 years at selected sites)

Change From

6.2.2. Days 1 and 2 ONLY for Sub-study Subjects (first 6 subjects aged 1 month to <2 years at selected sites)

- Pharmacokinetic sampling: ~~Five~~ **Six** blood samples (0.3-0.5 ml each) will be collected for anidulafungin measurement at the following time points:
 - On Day 1: 2 minutes before the end of infusion
 - **On Day 2:** just prior to the start of infusion, ~~88 minutes (equivalent to 2 minutes before the end of infusion)~~, 6 hours after start of infusion, 12 hours after start of infusion, and 24 hours after start of infusion.

In the event that –the sample required 2 minutes before the end of infusion was not taken at the specified time, every effort must be made to acquire a sample within 5 minutes of the end of infusion with proper and specific time documentation. Actual time of collection is to be documented in the CRF.

Note: In case the subjects are not ready for serial pharmacokinetic sampling on this specific day, this can be re-arranged at a later date when they continue to receive 1.5 mg/kg daily maintenance dose of anidulafungin. The flexibility of the sampling time is also allowed as long as the actual time of collection is recorded in the CRF.

Ideally, the pharmacokinetic (PK) sampling would be taken from a different site/line than the one used for study drug infusion. However, at the discretion of the investigator and with appropriate flushing of the line to clear all drug residues, samples may be collected using the same line.

Change To

6.2.2 Days 1 and 2 ONLY for Sub-study Subjects (first 6 subjects aged 1 month to <2 years at selected sites)

- Pharmacokinetic sampling: Six blood samples (0.3-0.5 ml each) will be collected for anidulafungin measurement at the following time points:
 - On Day 1: 2 minutes before the end of infusion
 - On Day 2: just prior to the start of infusion, 2 minutes before the end of infusion, 6 hours after start of infusion, 12 hours after start of infusion, and 24 hours after start of infusion.
 - In the event that the sample required 2 minutes before the end of infusion was not taken at the specified time, every effort must be made to acquire a sample within 5 minutes of the end of infusion with proper and specific time documentation.

Note: In case the subjects are not ready for serial pharmacokinetic sampling on this specific day, this can be re-arranged at a later date when they continue to receive 1.5 mg/kg daily maintenance dose of anidulafungin. The flexibility of the sampling time is also allowed as long as the actual time of collection is recorded in the CRF.

Ideally, the pharmacokinetic (PK) sampling would be taken from a different site/line than the one used for study drug infusion. However, at the discretion of the investigator and with appropriate flushing of the line to clear all drug residues, samples may be collected using the same line.

20. Section 6.2.3, Days 1, 3, 5, 7 and 9 for ALL subjects OTHER than the sub-study subjects above, Bullet 2

Change From

Days 1, 3, 5, 7 and 9 for ALL subjects OTHER than the sub-study subjects above

- Day 1: post-dose (between 0 – 2 hours following the end of anidulafungin infusion);

Change To

Day 1: post-dose (between 0 – 2 hours following the end of anidulafungin infusion);

21. Section 6.2.4 Day 3, Bullets 1,2,3,4

Change From

- Targeted physical examination;

- Blood cultures;
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);

Change To

- Targeted physical examination;
- Blood cultures;
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);

22. Section 6.2.5 Day 7, Bullets 1, 3, 4

Change From

- Targeted physical examination;
- Blood cultures;
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);

Change To

- Targeted physical examination;
- Blood cultures;
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);

23. Section 6.2.6, Day 10, Bullets 1, 3

Change From

- Targeted physical examination;
- Assessment of signs and symptoms of *Candida* infection;
- Blood cultures → to continue to be repeated every 3 days until two cultures separated by at least 24 hours are confirmed to be negative;

Change To

- Targeted physical examination;
- Assessment of signs and symptoms of *Candida* infection;
- Blood cultures;

24. Section 6.2.7, Days 11 to 34 (day prior to last day of IV anidulafungin therapy – maximum is 35 days on anidulafungin), Bullets 1, 3, 4

Change From

- Targeted physical examination every 3 days;
- Blood cultures → to continue to be repeated every 3 days until two cultures separated by at least 24 hours are confirmed to be negative;
- CBC with differential every seven days (**same as in screening**);
- Serum chemistry every seven days (**same as in screening**);

Change To

- Targeted physical examination every 3 days;
- Blood cultures → to continue to be repeated every 3 days until two cultures separated by at least 24 hours are confirmed to be negative;
- CBC with differential every seven days (same as in screening);
- Serum chemistry every seven days (same as in screening);

25. Section 6.3 End of IV anidulafungin therapy 1,5,6,7,8

Change From

- Targeted physical examination;
- Specimen culture ~~or microscopy~~ (from other normally sterile sites as clinically indicated);
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);
- Evaluation of Global Response (**see Section 7.2**);

Change To

- Targeted physical examination;
- Specimen culture (from other normally sterile sites as clinically indicated);
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);
- Evaluation of Global Response (see Section 7.2);

26. Section 6.4, End of Oral therapy (if applicable), Bullets 1,6,7,8

Change From

- Targeted physical examination;
- Specimen culture ~~or microscopy~~ (from other normally sterile sites as clinically indicated);
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);
- Evaluation of Global Response (see Section 7.2);

Change To

- Targeted physical examination;
- Specimen culture (from other normally sterile sites as clinically indicated);
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);
- Evaluation of Global Response (see Section 7.2);

27. Section 6.5 Follow up Visit (End of Treatment + 2 weeks), Bullet 1,6,7,8,9,10

Change From

- Targeted physical examination;
- Specimen culture ~~or microscopy~~ (from other normally sterile sites as clinically indicated);

- CBC with differential (**same as in screening**) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;
- Serum chemistry (**same as in screening**) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;
- Evaluation of Global Response (see Section 7.2);
- Record Adverse Events.

Change To

- Targeted physical examination;
- Specimen culture (from other normally sterile sites as clinically indicated);
- CBC with differential (same as in screening) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;
- Serum chemistry (same as in screening) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;
- Evaluation of Global Response (see Section 7.2);
- Record Adverse Events.

28. Section 6.6, Long term follow-up (End of Treatment + 6 weeks), Bullets 1,6,7,8,9,10

Change From

- Targeted physical examination;
- Specimen culture ~~or microscopy~~ (from other normally sterile sites as clinically indicated);
- CBC with differential (**same as in screening**) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;
- Serum chemistry (**same as in screening**) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;
- Evaluation of Global Response (see Section 7.2);
- Record Adverse Events.

Change To

- Targeted physical examination;
- Specimen culture (from other normally sterile sites as clinically indicated);
- CBC with differential (same as in screening) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;
- Serum chemistry (same as in screening) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;
- Evaluation of Global Response (see Section 7.2);
- Record Adverse Events.

29. Section 7.1 Microbiological Response, Success, Failure, Indeterminate

Change From

Microbiological Response

Success:

- **Eradication or presumed eradication:** Baseline pathogen not isolated from original site culture(s), **or culture data are not;**
- ~~Presumed eradication: will be i~~ **available for a subject with successful outcome** ~~ferred in subjects with complete clinical and imaging response for whom an invasive procedure for obtaining the relevant clinical specimen is not performed.~~

Failure:

- **Persistence (documented or presumed): Any baseline *Candida* spp. is present in repeat cultures, or culture data are not available for subject with a clinical outcome of failure** ~~Baseline pathogen isolated from original site culture(s).~~

Indeterminate:

- **Culture data are not available for a subject with a clinical outcome of indeterminate.** ~~Inadequate data available for categorization as eradication, presumed eradication or persistence.~~

The following definitions will be used for assessments made at the FU visits:

- a. Relapse: Subjects who were considered improved or completely resolved of infection at the end of treatment evaluation who now present with new or worsened signs and symptoms due to *Candida* infection at the same site that was previously infected. **Any baseline *Candida* spp 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.

b. New Infection: Subject presenting with clinical failure during the study with the emergence of new *Candida* spp at the original site of infection or at a distant site of infection ~~Subjects who were considered improved or completely resolved of infection at the end of treatment evaluation who now present with new or worsened signs and symptoms due to *Candida* infection at a different site from the site previously infected.~~

c. Continued Complete Resolution/Improvement: Subjects who are evaluated as completely resolved of infection or improved at the end of treatment evaluation and whose condition remains stable at the follow-up evaluation.

In addition, subjects will be contacted (eg, in person, by telephone, mail, or e-mail) to determine survival status at 2-Week and 6-Week after EOT. If a subject cannot be contacted, survival status may be obtained through a family member, hospital/clinic records or information that is in the public domain.

Change To

Microbiological Response

Success:

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

Failure:

- Persistence (documented or presumed): Any baseline *Candida* spp. 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.

The following definitions will be used for assessments made at the FU visits:

a. Relapse: Any baseline *Candida* spp 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;

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

c. Continued Complete Resolution/Improvement: Subjects who are evaluated as completely resolved of infection or improved at the end of treatment evaluation and whose condition remains stable at the follow-up evaluation.

In addition, subjects will be contacted (eg, in person, by telephone, mail, or e-mail) to determine survival status at 2-Week and 6-Week after EOT. If a subject cannot be contacted, survival status may be obtained through a family member, hospital/clinic records or information that is in the public domain.

30. Section 7.2, Safety Assessments, Paragraph 1

Change From

All subjects who receive at least one dose of study medication will be evaluated for safety. Safety will be assessed at each visit through physical examination, assessment of laboratory parameters and assessment of adverse events. **It will be particularly important for investigators to carefully monitor subjects for any adverse events, including elevations in liver function tests, that could be related to anidulafungin.**

Change To

All subjects who receive at least one dose of study medication will be evaluated for safety. Safety will be assessed at each visit through physical examination, assessment of laboratory parameters and assessment of adverse events. It will be particularly important for investigators to carefully monitor subjects for any adverse events, including elevations in liver function tests, that could be related to anidulafungin.

31. Section 7.3.1 Hematology and Blood Chemistry

Change From

Addition

7.3.1. Hematology and Blood Chemistry

The study sites will process routine hematology and blood chemistry specimens locally.

Change To

7.3.1. Hematology and Blood Chemistry

The study sites will process routine hematology and blood chemistry specimens locally.

32. Section 7.3.2. Diagnostic Testing for *Candida* Infection

Addition

7.3.2. Diagnostic Testing for *Candida* Infection

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

33. Section 7.3.3 Microbiological Determinations

Change From

7.3.3. Microbiological Determinations

1. Screening Blood Cultures: Two (2) aerobic blood cultures from 2 different sites will be performed at screening on all subjects. If the screening positive baseline culture was drawn ~~is~~ >96 hours before the start of treatment, the blood cultures should be repeated. If the screening blood samples for cultures were taken ~~are~~ <96 hours before study entry, blood cultures do not need to be repeated. Peripheral venipuncture is the preferred method for obtaining blood cultures.
2. Baseline Cultures (other than blood): Obtained as clinically indicated.
3. On-Study Cultures:
 - a. Blood cultures will be repeated on Days 3, ~~and~~ 7, 10 and every third day thereafter until two cultures separated by at least 24 hours are confirmed to be negative **while on study medication, at the end of IV therapy, end of oral therapy, and at the early and late follow-up visits. Additional cultures may be obtained at the investigator's discretion as clinically indicated.** ~~Specimen cultures or microscopy of other normally sterile sites are to be repeated daily during the trial.~~
 - b. Other than Blood: For subjects whose baseline isolates (or histological evidence of infection) were obtained from samples other than blood, culture or histology from the same site should be repeated as clinically indicated.

Investigators will send specimens (blood or other) to their local certified laboratory for culture (incubation should be a minimum of five days if not positive before then). Each laboratory will follow its usual procedures for identification of the species and susceptibility testing to marketed antifungal agents.

Additionally, all *Candida* isolates must be preserved for shipment to the reference laboratory for further identification, including speciation, and susceptibility testing. This includes the original isolate that the diagnosis for inclusion into the study was made. If more than one species of *Candida* is isolated from a single culture, all isolates must be sent to the reference laboratory. The susceptibility testing will be conducted using the current Clinical and Laboratory Standards Institute (CLSI) approved standard method.

Change To

7.3.3. Microbiological Determinations

1. Screening Blood Cultures: Two (2) aerobic blood cultures from 2 different sites will be performed at screening on all subjects. If the screening positive baseline culture was drawn > 96 hours before the start of treatment, the blood cultures should be repeated. If the screening blood samples for culture were taken <96 hours before study entry, blood cultures do not need to be repeated. Peripheral venipuncture is the preferred method for obtaining blood cultures.
2. Baseline Cultures (other than blood): Obtained as clinically indicated.
3. On-Study Cultures:
 - a. Blood cultures will be repeated on Days 3, 7, 10 and every third day thereafter until two cultures separated by at least 24 hours are confirmed to be negative while on study medication, at the end of IV therapy, end of oral therapy, and at the early and late follow-up visits. Additional cultures may be obtained at the investigator's discretion as clinically indicated.
 - b. Other than Blood: For subjects whose baseline isolates (or histological evidence of infection) were obtained from samples other than blood, culture or histology from the same site should be repeated as clinically indicated.

Investigators will send specimens (blood or other) to their local certified laboratory for culture (incubation should be a minimum of five days if not positive before then). Each laboratory will follow its usual procedures for identification of the species and susceptibility testing to marketed antifungal agents.

Additionally, all *Candida* isolates must be preserved for shipment to the reference laboratory for further identification, including speciation, and susceptibility testing. This includes the original isolate that the diagnosis for inclusion into the study was made. If more than one species of *Candida* is isolated from a single culture, all isolates must be sent to the reference laboratory. The susceptibility testing will be conducted using the current Clinical and Laboratory Standards Institute (CLSI) approved standard method.

34. Section 7.4, Pharmacokinetic Assessments

Change From

Plasma for analysis of anidulafungin

In the first 6 children aged <2 years, to be enrolled at selected centers, blood samples (approximately 0.3 - 0.5 mL each) will be collected for anidulafungin measurement at the following ~~65~~ time points. **On Day 1 (receiving 3 mg/kg IV infusion): 2 minutes before the end of infusion;** on Day 2 (receiving 1.5 mg/kg IV infusion ~~over 1.5 hours~~): just prior to the start of infusion, ~~88 minutes (equivalent to 2 minutes before the end of infusion)~~, 6, 12 and 24 hours after the start of infusion.

Due to the special conditions of the study population, the sampling time and day can be flexible in order to fit the subject's schedule. For instance, if serial pharmacokinetic sampling cannot be scheduled on Day 2, subjects will continue to remain on IV treatment to allow sample collection at a later date. The actual sampling time and date will be recorded in the CRF.

In addition, in order to ensure there is no assay interference in these 6 subjects, it is recommended to send a blank serum sample (0.1 - 0.2 mL), ~~small amount left from the Screening safety lab test if available~~ from these subjects to the assay laboratory for potential interference check. This small amount may be left from the Screening safety lab test if available; otherwise it should be collected.

Blood samples (approximately 0.3 - 0.5 mL each) will also be collected at 3 - ~~45~~ of the following occasions during the study for all subjects (except for the first 6 subjects enrolled in the 1 month - <2 year age group):

- **Day 1: Post-dose (between 0-2 hours following the end of anidulafungin infusion);**
- Day 3: Pre-dose (just prior to the start of anidulafungin infusion);
- Day 5: Post-dose (between 0-3 hours following the end of anidulafungin infusion);
- Day 7: Delayed post-dose (between 6-12 hours following the end of anidulafungin infusion);
- Day 9: Pre-dose (just prior to the start of anidulafungin infusion).

The above sampling days are flexible and could be modified at the discretion of each study center as long as samples are collected ~~between Day 2 and the last day of IV~~ **during the treatment period** with anidulafungin.

Blood samples will be centrifuged at approximately 1700 g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C within 1 hour of collection.

Plasma samples will be analyzed for anidulafungin using validated analytical methods in compliance with Pfizer standard operation procedures.

Change To

Plasma for analysis of anidulafungin

In the first 6 children aged <2 years, to be enrolled at selected centers, blood samples (approximately 0.3 - 0.5 mL each) will be collected for anidulafungin measurement at the following 6 time points. On Day 1 (receiving 3 mg/kg IV infusion): 2 minutes before the end of infusion; on Day 2 (receiving 1.5 mg/kg IV infusion): just prior to the start of infusion, 2 minutes before the end of infusion, 6, 12 and 24 hours after the start of infusion.

Due to the special conditions of the study population, the sampling time and day can be flexible in order to fit the subject's schedule. For instance, if serial pharmacokinetic sampling cannot be scheduled on Day 2, subjects will continue to remain on IV treatment to allow sample collection at a later date. The actual sampling time and date will be recorded in the CRF.

In addition, in order to ensure there is no assay interference in these 6 subjects, it is recommended to send a blank serum sample (0.1 - 0.2 mL) from these subjects to the assay laboratory for potential interference check. This small amount may be left from the Screening safety lab test if available; otherwise it should be collected.

Blood samples (approximately 0.3 - 0.5 mL each) will also be collected at 3 - 5 of the following occasions during the study for all subjects (except for the first 6 subjects enrolled in the 1 month - <2 year age group):

- Day 1: Post-dose (between 0-2 hours following the end of anidulafungin infusion);
- Day 3: Pre-dose (just prior to the start of anidulafungin infusion);
- Day 5: Post-dose (between 0-3 hours following the end of anidulafungin infusion);
- Day 7: Delayed post-dose (between 6-12 hours following the end of anidulafungin infusion);
- Day 9: Pre-dose (just prior to the start of anidulafungin infusion).

The above sampling days are flexible and could be modified at the discretion of each study center as long as samples are collected during the treatment period with anidulafungin.

Blood samples will be centrifuged at approximately 1700 g for about 10 minutes at 4°C. The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C within 1 hour of collection.

Plasma samples will be analyzed for anidulafungin using validated analytical methods in compliance with Pfizer standard operation procedures.

35. Section 8.9, Exposure In Utero, Numbers 1, 2, Paragraph 2

Change From

1. a female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure, **if appropriate**) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);
2. a male has been exposed, either due to treatment or environmental (**if appropriate**), to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to Pfizer on an Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure (**if appropriate**) to a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Change To

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure, if appropriate) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);
2. A male has been exposed, either due to treatment or environmental (if appropriate), to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to Pfizer on an Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure (if appropriate) to a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to a cytotoxic

product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

36. Section 9.1, Analysis of Primary Endpoint, Paragraphs 1, 3

Change From

The primary analysis will be the evaluation of adverse events throughout the trial, laboratory tests, **and** physical examination, **signs and symptoms, temperature, and fundoscopic examination.**

The following parameters will be summarized: rates of discontinuation, adverse events, **and** laboratory abnormalities, ~~changes in temperature, signs and symptoms, and changes in fundoscopic examination (if applicable).~~

Change To

The primary analysis will be the evaluation of adverse events throughout the trial, laboratory tests, and physical examination.

The following parameters will be summarized: rates of discontinuation, adverse events, and laboratory abnormalities.

37. Section 9.2, Analysis of Secondary Endpoints

Change From

~~The main~~ efficacy analysis will be an assessment of global response **at EOIVT, EOT , 2 week and 6 week FU visits at EOT.** The ~~primary~~ analysis will be conducted by frequencies and percentages of global response by determination (success, failure). ~~Secondary-These~~ efficacy analyses will be assessed in the Modified Intent-to-Treat (MITT) population, which will be defined as all subjects who have received at least one dose of study drug and who have microbiological evidence of *Candida species* infection.

Supportive analyses of the main efficacy endpoint ~~at EOT~~ will be performed in the Intent to Treat (ITT) population, consisting of all randomized subjects.

Other analyses will include ~~rate of global response at the EOIVT and FU visits,~~ rates of relapse and emerging infection at FU visits, and ~~all-cause mortality rates at EOIVT and EOT, using the similar methods as described above-~~ **analysis of time to death to determine all-cause mortality rates.**

Change To

The efficacy analysis will be an assessment of global response at EOIVT, EOT, 2 week and 6 week FU visits. The analysis will be conducted by frequencies and percentages of global response by determination (success, failure). These efficacy analyses will be assessed in the Modified Intent-to-Treat (MITT) population, which will be defined as all subjects who have received at least one dose of study drug and who have microbiological evidence of *Candida* infection.

Supportive analyses of the main efficacy endpoint will be performed in the Intent to Treat (ITT) population, consisting of all randomized subjects.

Other analyses will include rates of relapse and emerging infection at FU visits, and analysis of time to death to determine all-cause mortality rates.

38. Section 9.3.1. Non-compartmental Pharmacokinetic Analysis

Change From

Non-compartmental pharmacokinetic analysis will be performed on individual plasma anidulafungin concentration-time data from children <2 years ~~using WinNonlin (V.3.2, Pharsight®, Mountain View, CA)~~ to obtain the following pharmacokinetic parameters of anidulafungin: AUC₂₄ and C_{max}. Data listings and summary statistics will be generated for each pharmacokinetic parameter and presented in graphical and/or tabular format.

Change To

Non-compartmental pharmacokinetic analysis will be performed on individual plasma anidulafungin concentration-time data from children <2 years to obtain the following pharmacokinetic parameters of anidulafungin: AUC₂₄ and C_{max}. Data listings and summary statistics will be generated for each pharmacokinetic parameter and presented in graphical and/or tabular format.

39. Section 9.3.2, Population Pharmacokinetic-Pharmacodynamic (PK-PD) Analysis

Change From

Measures of efficacy or safety versus steady-state anidulafungin exposure (AUC₂₄) will be modeled using a nonlinear mixed effects approach ~~(NONMEM software, version V level 1.1, GloboMax, Ellicott City/Hanover, MD)~~ as appropriate.

Firstly, population pharmacokinetic analysis on the plasma concentration data of anidulafungin will be performed ~~using NONMEM~~ to derive the conditional estimation of individual AUC₂₄.

Population PK-PD models will be developed using an iterative process, adapting the model to improve the goodness of fit. In the case that only one record on the PD data (efficacy or safety endpoints) will be obtained from each subject, a naïve pooled data (NPD) analysis will be considered for PK-PD analysis. In the case that multiple measurements are available, the time to event analysis may be explored as appropriate.

If a sufficient number of MIC values are available, the association between the PK-PD index, AUC/MIC, and efficacy will also be evaluated using the same approach. **If data permit, the association between C_{\max} /MIC and efficacy will be explored.**

Change To

Measures of efficacy or safety versus steady-state anidulafungin exposure (AUC_{24}) will be modeled using a nonlinear mixed effects approach as appropriate.

Firstly, population pharmacokinetic analysis on the plasma concentration data of anidulafungin will be performed to derive the conditional estimation of individual AUC_{24} .

Population PK-PD models will be developed using an iterative process, adapting the model to improve the goodness of fit. In the case that only one record on the PD data (efficacy or safety endpoints) will be obtained from each subject, a naïve pooled data (NPD) analysis will be considered for PK-PD analysis. In the case that multiple measurements are available, the time to event analysis may be explored as appropriate.

If a sufficient number of MIC values are available, the association between the PK-PD index, AUC/MIC, and efficacy will also be evaluated using the same approach. If data permit, the association between C_{\max} /MIC and efficacy will be explored.

40. Section, 12.3 Subject Information and Consent, Paragraph 4

Change From

The investigator must ensure that each study subject, **and**/or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject's legally acceptable representative and assent from each subject (if applicable) before any study-specific activity is performed. The investigator will retain the original of each subject's assent form (if applicable) and his/her legally acceptable representative's signed consent form.

Change To

The investigator must ensure that each study subject, and/or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject's legally acceptable representative and assent from each subject (if applicable) before any study-specific activity

is performed. The investigator will retain the original of each subject's assent form (if applicable) and his/her legally acceptable representative's signed consent form.

41. Section 14, SPONSOR DISCONTINUATION CRITERIA, Paragraph 1

Change From

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems (**such as repeated sever or serious AEs warranting temporary or permanent study termination**), or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of anidulafungin at any time.

Change To

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems (such as repeated sever or serious AEs warranting temporary or permanent study termination), or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of anidulafungin at any time.

Appendix 2. CLINICAL PROTOCOL AMENDMENT 2

<u>Current Amendment:</u>			
Amendment No. Amendment 2	Date 02 July 2008	Country (ies)	Site(s)
<u>Previous Amendments:</u>			
Amendment No. Amendment 1	Date 12 March 2008	Country (ies)	Site(s)

SUMMARY**Reason(s) for Amendment**

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

- The “change from” section represents the current text in the protocol. **Bolded** text is used to indicate the addition of information to the current text, and strike-out of text (eg, ~~text~~) is used to show the deletion of information from the current text.
- The “change to” section represents the revised text, with the revisions shown in the “change from” section in normal text.

1. SECTION PROTOCOL SUMMARY, Paragraph 2

CHANGE FROM

The primary study objective is to assess the safety and tolerability of anidulafungin when used to treat children with (ICC). Additional assessments will include global response at the end of IV therapy (EOIVT) and subsequent time points, exposure-response relationship, the rates of relapse and ~~newemerging~~ infection at follow up (FU) visits, and analysis of time to death during study therapy and follow-up visits.

CHANGE TO

The primary study objective is to assess the safety and tolerability of anidulafungin when used to treat children with (ICC). Additional assessments will include global response at the end of IV therapy (EOIVT) and subsequent time points, exposure-response relationship, the rates of relapse and new infection at follow up (FU) visits, and analysis of time to death during study therapy and follow-up visits.

24. 2. SECTION PROTOCOL SUMMARY STUDY DESIGN, Paragraph 4, 8

CHANGE FROM

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine or ~~serum~~ pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated on Days 3 and 7 and every third day thereafter until two cultures separated by at least 24 hours are confirmed to be negative. Any negative blood culture after Day 1 (per protocol schedule or otherwise) must be repeated after 24 hours.

We plan to amend this protocol at a future time to allow for the enrollment of neonates (from 0 to 1 month of age) when additional pharmacokinetic data are available for this patient population.

CHANGE TO

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine or serum pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated on Days 3 and 7 and every third day thereafter until two cultures separated by at least 24 hours are confirmed to be negative. Any negative blood culture after Day 1 (per protocol schedule or otherwise) must be repeated after 24 hours.

We plan to amend this protocol at a future time to allow for the enrollment of neonates (from 0 to 1 month of age) when additional pharmacokinetic data are available for this patient population.

3. SECTION PROTOCOL SUMMARY OBJECTIVES SECONDARY, *Bullet 5*

CHANGE FROM

- To assess rates of ~~newemerging~~ infection at the Week 2 and Week 6 FU visits;

CHANGE TO

- To assess rates of new infection at the Week 2 and Week 6 FU visits;

4. SECTION PROTOCOL SUMMARY ENDPOINTS SECONDARY, *Bullet 5*

CHANGE FROM

- Rates of ~~newemerging~~ infection at the Week 2 and Week 6 FU visits;

CHANGE TO

- Rates of new infection at the Week 2 and Week 6 FU visits;

5. SECTION PROTOCOL SUMMARY STATISTICAL METHODS, *Paragraph 1,4*

CHANGE FROM

The primary analysis will be the evaluation of adverse events throughout the trial, laboratory tests, **ECG findings (if applicable)**, temperature, and physical examination. The set of subjects for this evaluation will be the Safety population, defined as all subjects with at least 1 dose of study medication. The following parameters will be summarized: rates of discontinuation, adverse events, and laboratory abnormalities. Safety data will be descriptively summarized. Descriptive statistics for categorical data will include frequencies and/or percentages.

Other analyses will include rates of relapse and ~~newemerging~~ infection at FU visits, and analysis of time to death during study therapy and FU visits

25. CHANGE TO

The primary analysis will be the evaluation of adverse events throughout the trial, laboratory tests, ECG findings (if applicable), temperature, and physical examination. The set of subjects for this evaluation will be the Safety population, defined as all subjects with at least 1 dose of study medication. The following parameters will be summarized: rates of discontinuation, adverse events, and laboratory abnormalities. Safety data will be descriptively summarized. Descriptive statistics for categorical data will include frequencies and/or percentages.

Other analyses will include rates of relapse and new infection at FU visits, and analysis of time to death during study therapy and FU visits.

6. SECTION SCHEDULE OF ACTIVITIES

CHANGE FROM

Schedule of Activities

	Screening ¹	Daily through EOT	Day 3	Day 7	Day 10	Days 11-34	End of IV Therapy	End of Oral Therapy (if applicable)	Follow-Up Visit (EOT + 2 weeks) (± 2 days)	Long term Follow-Up (EOT + 6 weeks) (± 1 week)
Informed consent	X	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-
Complete physical examination (including vital signs) ²	X									
Targeted physical examination (Including vital signs)			X	X	X	Every 3 days	X	X	X	X
Temperature	X	X							X	X
Signs and symptoms	X				X		X	X	X	X
Urine pregnancy test ³	X						X	X		X
Fundoscopy exam	X						X ⁴	X ⁴	X ⁴	X ⁴
Blood cultures ⁵	X		X	X	X	X	X	X	X	X
Specimen culture ⁶	X	X						X	X	X
CBC with differential ⁷	X		X	X		Every 7 DaysX	X	X	X ⁸	X ⁸
Serum chemistry ⁷	X		X	X		Every 7 DaysX	X	X	X ⁸	X ⁸
Pharmacokinetic sampling (first 6 subjects 1 month to <2 yrs old) ^{9,10}		Days 1 and 2								

Pharmacokinetic sampling (all other subjects) ¹¹		Days 1, 3, 5, 7 and 9								
Study medication administration		X								
Adverse events		X							X	X
Concomitant medications		X								
Evaluation of Global Response							X	X	X	X
Follow up evaluation (relapse, new infection, or continued resolution/improvement)									X	X

1. Screening procedures/assessments are to be completed before the first dose of study medication.
2. May occur within 72 hours before the first dose of study medication.
3. For females of childbearing potential. This urine **or serum** pregnancy test is to be repeated at the end of therapy, IV or Oral, **and at the last follow up visit. Pregnancy tests may also be repeated as per request of IRB/IECs or as required by local regulations.**
4. To be completed only if the baseline fundoscopic examination was ~~positive for endophthalmitis.~~ **abnormal.**
5. Screening blood culture is to be obtained within 96 hours before first dose of Study Drug (Day 1). Blood cultures will be repeated on Day 3, 7, and every three days until 2 cultures separated by at least 24 hours are confirmed to be negative while on study medication and as clinically indicated. Pathogen isolated will be documented.
6. Cultures of other normally sterile sites as clinically indicated. Pathogen isolated will be documented.
7. CBC with differential (including RBC count and platelets count), and serum chemistry tests (AST, ALT, Alk-Phos, total Bilirubin, Albumin, BUN, Cr, Bicarbonate, Glucose, Na, K, Ca, Cl, Mg) are to be repeated on Day 3, 7 and every seven days during treatment phase, and repeated at **both** the follow-up visits ~~if clinically significant abnormalities were present on the last day of study medication.~~
8. Hematology and chemistry tests should be repeated at **both** the follow-up visits ~~if clinically significant abnormalities were present on the last day of study medication.~~
9. Six blood samples (0.3 - 0.5 mL each) will be collected for anidulafungin measurement at the following time points in the first 6 subjects: on Day 1 (receiving 3.0 mg/kg IV infusion): 2 minutes before the end of infusion); on Day 2 (receiving 1.5 mg/kg IV infusion): just prior to the start of infusion, 2 minutes before the end of infusion, and 6, 12 and 24 hours after the start of infusion. Exact sampling times may be modified to accommodate subject schedules provided that the actual time of collection is documented in the Case Report Form (CRF).
10. For the first 6 subjects aged 1 month to <2 years, use of a second systemic antifungal agent (eg, amphotericin B) will be permitted (these subjects will be enrolled at selected centers).
11. Samples (0.3 - 0.5 mL each) will be collected for anidulafungin measurement at 3-5 of the following occasions during the study: Day 1: Post-dose (between 0-2 hours following the end of anidulafungin infusion); Day 3: Pre-dose (just prior to the start of anidulafungin infusion); Day 5: Post-dose (between 0-3 hours following the end of anidulafungin infusion); Day 7: Delayed post-dose (between 6-12 hours following the end of anidulafungin infusion); Day 9: Pre-dose (just prior to the start of anidulafungin infusion). Exact sampling times may be modified to accommodate subject schedules as long as the samples are collected during the IV treatment period.

CHANGE TO

Schedule of Activities

	Screening ¹	Daily through EOT	Day 3	Day 7	Day 10	Days 11-34	End of IV Therapy	End of Oral Therapy (if applicable)	Follow-Up Visit (EOT + 2 weeks) (± 2 days)	Long term Follow-Up (EOT + 6 weeks) (± 1 week)
Informed consent	X	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-
Complete physical examination (including vital signs) ²	X									
Targeted physical examination (Including vital signs)			X	X	X	Every 3 days	X	X	X	X
Temperature	X	X							X	X
Signs and symptoms	X				X		X	X	X	X
Urine pregnancy test ³	X						X	X		X
Fundoscopy exam	X						X ⁴	X ⁴	X ⁴	X ⁴
Blood cultures ⁵	X		X	X	X	X	X	X	X	X
Specimen culture ⁶	X	X						X	X	X
CBC with differential ⁷	X		X	X		Every 7 days	X	X	X ⁸	X ⁸
Serum chemistry ⁷	X		X	X		Every 7 Days	X	X	X ⁸	X ⁸
Pharmacokinetic sampling (first 6 subjects 1 month to <2 weeks) ^{9,10}		Days 1 and 2								
Pharmacokinetic sampling (all other subjects) ¹¹		Days 1, 3, 5, 7 and 9								

Study medication administration		X								
Adverse events		X							X	X
Concomitant medications		X								
Evaluation of Global Response							X	X	X	X
Follow up evaluation (relapse, new infection, or continued resolution/improvement)									X	X

1. Screening procedures/assessments are to be completed before the first dose of study medication.
2. May occur within 72 hours before the first dose of study medication.
3. For females of childbearing potential. This urine or serum pregnancy test is to be repeated at the end of therapy, IV or Oral, and at the last follow up visit. Pregnancy tests may also be repeated as per request of IRB/IECs or as required by local regulations..
4. To be completed only if the baseline fundoscopic examination was abnormal.
5. Screening blood culture is to be obtained within 96 hours before first dose of Study Drug (Day 1). Blood cultures will be repeated on Day 3, 7, and every three days until 2 cultures separated by at least 24 hours are confirmed to be negative while on study medication and as clinically indicated. Pathogen isolated will be documented.
6. Cultures of other normally sterile sites as clinically indicated. Pathogen isolated will be documented.
7. CBC with differential (including RBC count and platelets count), and serum chemistry tests (AST, ALT, Alk-Phos, total Bilirubin, Albumin, BUN, Cr, Bicarbonate, Glucose, Na, K, Ca, Cl, Mg) are to be repeated on Day 3, 7 and every seven days during treatment phase, and repeated at both follow-up visits.
8. Hematology and chemistry tests should be repeated at both follow-up visits.
9. Six blood samples (0.3 - 0.5 mL each) will be collected for anidulafungin measurement at the following time points in the first 6 subjects: on Day 1 (receiving 3.0 mg/kg IV infusion): 2 minutes before the end of infusion); on Day 2 (receiving 1.5 mg/kg IV infusion): just prior to the start of infusion, 2 minutes before the end of infusion, and 6, 12 and 24 hours after the start of infusion. Exact sampling times may be modified to accommodate subject schedules provided that the actual time of collection is documented in the Case Report Form (CRF).
10. For the first 6 subjects aged 1 month to <2 years, use of a second systemic antifungal agent (eg, amphotericin B) will be permitted (these subjects will be enrolled at selected centers).
11. Samples (0.3 - 0.5 mL each) will be collected for anidulafungin measurement at 3-5 of the following occasions during the study: Day 1: Post-dose (between 0-2 hours following the end of anidulafungin infusion); Day 3: Pre-dose (just prior to the start of anidulafungin infusion); Day 5: Post-dose (between 0-3 hours following the end of anidulafungin infusion); Day 7: Delayed post-dose (between 6-12 hours following the end of anidulafungin infusion); Day 9: Pre-dose (just prior to the start of anidulafungin infusion). Exact sampling times may be modified to accommodate subject schedules as long as the samples are collected during the IV treatment period.

7. SECTION 2.1 OBJECTIVES, SECONDARY, Bullet 5

CHANGE FROM

To assess rates of ~~emerging~~ **new** infection at the Week 2 and Week 6 FU visits;

CHANGE TO

To assess rates of new infection at the Week 2 and Week 6 FU visits;

8. SECTION 2.2 ENDPOINTS, SECONDARY, Bullet 5

CHANGE FROM

Rates of ~~emerging~~ **new** infection at the Week 2 and Week 6 FU visits;

CHANGE TO

Rates of new infection at the Week 2 and Week 6 FU visits;

9. SECTION 3. STUDY DESIGN, Paragraph 5 and Addition of Paragraph 9

CHANGE FROM

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine **or serum** pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated on Days 3 and 7 and every third day thereafter until two cultures separated by at least 24 hours are confirmed to be negative. If blood cultures are performed more frequently than required by the protocol; a second blood culture after 24 hours of any negative culture is required.

We plan to amend this protocol at a future time to allow for the enrollment of neonates (from 0 to 1 month of age) when additional pharmacokinetic data are available for this patient population.

CHANGE TO

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine or serum pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated on Days 3 and 7 and every third day thereafter until two cultures separated by at least 24 hours are confirmed to be negative. If blood cultures are performed more frequently than required by the protocol; a second blood culture after 24 hours of any negative culture is required.

We plan to amend this protocol at a future time to allow for the enrollment of neonates (from 0 to 1 month of age) when additional pharmacokinetic data are available for this patient population.

10. SECTION 4.1 INCLUSION CRITERIA, List Number 2

CHANGE FROM

2. Male or female between the ages of 1 month and <18 years. Females of childbearing potential must have adequate contraception as determined by the Investigator for the duration of the trial.

CHANGE TO

2. Male or female between the ages of 1 month and <18 years. Females of childbearing potential must have adequate contraception as determined by the Investigator for the duration of the trial.

11. SECTION 4.2 EXCLUSION CRITERIA, List Number 14

CHANGE FROM

14. Other severe acute or chronic medical or psychiatric condition, **electrocardiogram (ECG) abnormalities**, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

CHANGE TO

14. Other severe acute or chronic medical or psychiatric condition, electrocardiogram (ECG) abnormalities, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

12. SECTION 5.1 ALLOCATION TO TREATMENT, Paragraph 4

CHANGE FROM

All subjects will receive IV anidulafungin. **For dosing purposes younger subjects must be weighed frequently (such as daily), but less frequently for older children as determined by the investigator.** 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. Total treatment duration with anidulafungin is not to exceed 35 days. After a minimum of 10 days of treatment with IV anidulafungin, subjects

may be switched to oral fluconazole (6 – 12 mg/kg/day, maximum 800 mg/day) provided that all of the following criteria are met:

CHANGE TO

All subjects will receive IV anidulafungin. For dosing purposes younger subjects must be weighed frequently (such as daily), but less frequently for older children as determined by the investigator. 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. Total treatment duration with anidulafungin is not to exceed 35 days. After a minimum of 10 days of treatment with IV anidulafungin, subjects may be switched to oral fluconazole (6 – 12 mg/kg/day, maximum 800 mg/day) provided that all of the following criteria are met:

13. SECTION 5.2.1. FORMULATION AND PACKAGING, STUDY DRUG PACKAGING

CHANGE FROM

Packaging: Anidulafungin (Eraxis™) for Injection will be supplied as an investigational product by the Pfizer Supply Chain. ~~Chain in a single use vial of sterile, lyophilized powder containing 100 mg of anidulafungin. Fifteen (15) single use vials will be supplied to each participating study site in anticipation of subject enrollment. Upon successful enrollment, an additional thirty-six (36) single use vials will be supplied to the site for each subject's anticipated study treatment and to replenish the original site inventory.~~ Anidulafungin for injection will be packaged and labeled to meet study-specific and regulatory requirements. Written Dosing Administration Instructions (DAI) will be provided that describe the method for reconstitution and further dilution of anidulafungin in preparation for administration.

CHANGE TO

Packaging: Anidulafungin (Eraxis™) for Injection will be supplied as an investigational product by the Pfizer Supply Chain. Anidulafungin for injection will be packaged and labeled to meet study-specific and regulatory requirements. Written Dosing Administration Instructions (DAI) will be provided that describe the method for reconstitution and further dilution of anidulafungin in preparation for administration.

14. SECTION 5.2.1. FORMULATION AND PACKAGING, STUDY DRUG PACKAGING

CHANGE FROM

Oral Medication

Generic Name: Fluconazole

Trade Name: ~~_____~~ Diflucan®

Dosage Form: Oral tablets and oral suspension

Strength: Oral tablets containing 50, 100, 150, or 200 mg of fluconazole.
Oral Suspension containing 350 mg or 1400 mg of fluconazole.

Manufacturer: Pfizer Inc.

Clinical Supply

Packaging: Each participating site is responsible to procure commercially packaged Diflucan (fluconazole) tablets and oral suspension as needed.

Note: If applicable, the site can use the locally available capsule formulation of fluconazole.

CHANGE TO

Oral Medication

Generic Name: Fluconazole

Dosage Form: Oral tablets and oral suspension

Strength: Oral tablets containing 50, 100, 150, or 200 mg of fluconazole.
Oral Suspension containing 350 mg or 1400 mg of fluconazole.

Manufacturer: Pfizer Inc.

Clinical Supply

Packaging: Each participating site is responsible to procure commercially packaged fluconazole tablets and oral suspension as needed.

Note: If applicable, the site can use the locally available capsule formulation of fluconazole.

15. SECTION SECTION 6. STUDY PROCEDURES, Paragraph 2

CHANGE FROM

Witnessed written parental or legal guardian consent and assent from the child or adolescent must be obtained prior to performing any screening procedures. Subject identification numbers will be assigned sequentially as subjects are screened into the study using a telephone/web-based system, and these numbers will be retained throughout the study.

CHANGE TO

Witnessed written parental or legal guardian consent and assent from the child or adolescent must be obtained prior to performing any screening procedures. Subject identification numbers will be assigned sequentially as subjects are screened into the study and these numbers will be retained throughout the study.

16. SECTION 6.1. SCREENING VISIT, Bullet 6

CHANGE FROM

Urine **or serum** pregnancy test (for females of childbearing potential);

CHANGE TO

Urine or serum pregnancy test (for females of childbearing potential);

17. SECTION 6.2.3. DAYS 1, 3, 5, 7, AND 9 FOR ALL SUBJECTS OTHER THAN THE SUB-STUDY SUBJECTS ABOVE, Bullet 6 Note

CHANGE FROM

Note: The above sampling days are flexible and could be modified at the discretion of each study center as long as samples are collected between Day **12** and the last day of IV treatment with anidulafungin with the actual time of collection documented in the CRF.

CHANGE TO

Note: The above sampling days are flexible and could be modified at the discretion of each study center as long as samples are collected between Day 1 and the last day of IV treatment with anidulafungin with the actual time of collection documented in the CRF.

18. SECTION 6.2.4. DAY 3, Bullet 1

CHANGE FROM

- Targeted physical examination (**including vital signs**);

CHANGE TO

- Targeted physical examination (including vital signs);

19. SECTION 6.2.5. DAY 7, Bullet 1, 5

CHANGE FROM

Targeted physical examination **(including vital signs)**;

CHANGE TO

Targeted physical examination (including vital signs);

20. SECTION 6.2.6. DAY 10, Bullet 1

CHANGE FROM

- Targeted physical examination **(including vital signs)**;

CHANGE TO

- Targeted physical examination (including vital signs);

21. SECTION 6.2.7. DAYS 11 TO 34 (DAY PRIOR TO LAST DAY OF IV ANIDULAFUNGIN THERAPY – MAXIMUM IS 35 DAYS ON ANIDULAFUNGIN), Bullet 1

CHANGE FROM

- Targeted physical examination **(including vital signs)** every 3 days;

CHANGE TO

- Targeted physical examination (including vital signs) every 3 days;

22. SECTION 6.3. END OF IV ANIDULAFUNGIN THERAPY, Bullet 1, 3

CHANGE FROM

- Targeted physical examination **(including vital signs)**;
- Fundoscopic examination only if the baseline fundoscopic examination was **abnormal** ~~positive for endophthalmitis~~.

CHANGE TO

- Targeted physical examination (including vital signs);
- Fundoscopic examination only if the baseline fundoscopic examination was abnormal.

23. SECTION 6.4. END OF ORAL THERAPY (IF APPLICABLE), Bullet 1, 3

CHANGE FROM

- Targeted physical examination **(including vital signs)**
- Fundoscopic examination only if the baseline fundoscopic examination was **abnormal** ~~positive for endophthalmitis~~.

CHANGE TO

- Targeted physical examination (including vital signs);
- Fundoscopic examination only if the baseline fundoscopic examination was abnormal.

24. SECTION 6.5. FOLLOW UP VISIT (END OF TREATMENT + 2 WEEKS), Bullet 1, 4, 7, 8

CHANGE FROM

- Targeted physical examination **(including vital signs)**;
- Fundoscopic examination only if the baseline fundoscopic examination was **abnormal** ~~positive for endophthalmitis~~.
- CBC with differential (same as in screening) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;
- Serum chemistry (same as in screening) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;

CHANGE TO

- Targeted physical examination (including vital signs);
- Fundoscopic examination only if the baseline fundoscopic examination was abnormal.
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);

25. SECTION 6.6. LONG TERM FOLLOW-UP (END OF TREATMENT + 6 WEEKS, Bullet 1, 4, 7, 8, 9

CHANGE FROM

- Targeted physical examination **(including vital signs)**;

- Fundoscopic examination only if the baseline fundoscopic examination was **abnormal** ~~positive for endophthalmitis~~.
- CBC with differential (same as in screening) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;
- Serum chemistry (same as in screening) only if clinically significant abnormalities were present when these labs were taken on the last day of study medication;
- Urine or serum pregnancy test (for females of childbearing potential).

CHANGE TO

- Targeted physical examination (including vital signs);
- Fundoscopic examination only if the baseline fundoscopic examination was abnormal.
- CBC with differential (same as in screening);
- Serum chemistry (same as in screening);
- Urine or serum pregnancy test (for females of childbearing potential).

26. SECTION 6.7. SUBJECT WITHDRAWAL, Paragraph 1

CHANGE FROM

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request **that** the subject ~~to~~ return all unused investigational product(s), request **that** the subject ~~to~~ return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

CHANGE TO

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

27. SECTION 7.1. CLINICAL ASSESSMENTS, Paragraph 1, a., b., and c.

Addition

All clinical assessments are to be performed by the Investigator and recorded in the subject's chart and the Case Report Form (CRF). It will be particularly important for Investigators to carefully monitor subjects for any Adverse Events that could be related to the study drug. Clinical assessments will include:

- a. Complete physical examination: height, weight, general appearance and vital signs (systolic and diastolic blood pressure, temperature, pulse and respiratory rates); cardiovascular system; abdomen and gastrointestinal system; urinary system; respiratory system; and central nervous system. Other examinations may also be performed at the discretion of the Investigator.
- b. Targeted physical examination: this is a simplified abbreviated and focused physical exam relevant to the patient's condition and progress as determined by the Investigator and includes the vital signs.
- c. Medical History: including (as appropriate) age, gender, medical history, surgical history, prior medications, adverse reactions to medications, and history of hepatic, renal, or cardiovascular systems.

28. SECTION 7.1. CLINICAL ASSESSMENTS, letter b., NEW INFECTION

CHANGE FROM

b. New Infection: Subject presenting with clinical failure ~~during the study~~ with the emergence of new *Candida* spp at the original site of infection or at a distant site of infection;

CHANGE TO

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

29. SECTION 7.2. ELECTROCARDIOGRAM (ECG) ADDED (SUBSEQUENT SECTION HEADINGS FOR SECTION 7 CHANGED AS A RESULT)

Addition

7.2. Electrocardiogram (ECG)

After the initiation of the first dose of anidulafungin, if a ventricular arrhythmia occur and assessed by the investigator as clinically significant, the investigator should collect a standard 12-lead electrocardiogram (ECG) at that time.

The investigator or a designated person will determine the appropriateness of the ECG recordings for interpretation. It may be necessary to repeat the ECG to obtain obtain readable tracing, calibrate the machine, or rule out improper lead placement. A printout of the ECG will be sent out to a central laboratory.

30. SECTION 7.5. PHARMACOKINETIC ASSESSMENTS, Paragraph 3

CHANGE FROM

In addition, in order to ensure there is no assay interference in these 6 subjects, it is recommended to send a blank ~~plasma serum~~ sample (0.1 - 0.2 mL) from these subjects to the assay laboratory for potential interference check. This small amount may be left from the Screening safety lab test if available; otherwise it should be collected.

CHANGE TO

In addition, in order to ensure there is no assay interference in these 6 subjects, it is recommended to send a blank plasma sample (0.1 - 0.2 mL) from these subjects to the assay laboratory for potential interference check. This small amount may be left from the Screening safety lab test if available; otherwise it should be collected.

31. SECTION 9.1. ANALYSIS OF PRIMARY ENDPOINT, Paragraph 3

CHANGE FROM

The following parameters will be summarized: rates of discontinuation, adverse events, **ECG findings (if applicable)**, and laboratory abnormalities.

CHANGE TO

The following parameters will be summarized: rates of discontinuation, adverse events, ECG findings (if applicable), and laboratory abnormalities.

32. SECTION 9.2. ANALYSIS OF SECONDARY ENDPOINTS, Paragraph 3

CHANGE FROM

Other analyses will include rates of relapse and ~~emerging-new~~ infection at FU visits, and analysis of time to death to determine all-cause mortality rates.

CHANGE TO

Other analyses will include rates of relapse and new infection at FU visits, and analysis of time to death to determine all-cause mortality rates.

33. SECTION 9.5. SAFETY ANALYSIS, Paragraph 1

CHANGE FROM

All subjects who have received at least 1 dose of study medication will be included in the safety analyses. Adverse events and other safety data, including **ECG (if applicable) and** laboratory data will be reviewed and summarized on an ongoing basis during the study. The Sponsor has standard algorithms for reporting adverse events and clinical laboratory test results, and these will be employed in the analysis of the data from this study. Safety and tolerability data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

CHANGE TO

All subjects who have received at least 1 dose of study medication will be included in the safety analyses. Adverse events and other safety data, including ECG (if applicable) and laboratory data will be reviewed and summarized on an ongoing basis during the study. The Sponsor has standard algorithms for reporting adverse events and clinical laboratory test results, and these will be employed in the analysis of the data from this study. Safety and tolerability data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Appendix 3. CLINICAL PROTOCOL AMENDMENT 3

Current Amendment: 3

Amendment No. 3	Date	Country (ies)	Site(s)
	21 September 2009		

Previous Amendments:

Amendment No. 2	Date	Country (ies)	Site(s)
	02 July 2008		

Amendment No. 1	Date	Country (ies)	Site(s)
	12 March 2008		

SUMMARY

Reason(s) for Amendment

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

The “change from” section represents the current text in the protocol. Bolded text is used to indicate the addition of information to the current text, and strike-out of text (eg, ~~text~~) is used to show the deletion of information from the current text.

The “change to” section represents the revised text, with the revisions shown in the “change from” section in normal text.

Section <Insert section number> , <Insert section title> , Page
<Insert page number as appropriate>

Change From

Change To

1. Section, PROTOCOL SUMMARY, 1st, 2nd paragraphs

Change From

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

The primary study objective is to assess the safety and tolerability of anidulafungin when used to treat children with (ICC). Additional assessments will include global response at the end of IV therapy (EOIVT) and subsequent time points, exposure-response relationship, the rates of relapse (**recurrence**) and new infection at follow up (FU) visits, and analysis of time to death during study therapy and follow-up visits.

Change To

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

The primary study objective is to assess the safety and tolerability of anidulafungin when used to treat children with ICC. Additional assessments will include global response at the end of IV therapy (EOIVT) and subsequent time points, exposure-response relationship, the rates of relapse (recurrence) and new infection at follow up (FU) visits, and analysis of time to death during study therapy and follow-up visits.

2. Section, PROTOCOL SUMMARY, Background and Rationale, 1st, 2nd paragraphs references added, 3rd paragraph

Change From

The incidence of systemic invasive fungal infections has risen significantly in the past decade. Infections due to *Candida* spp. account for about 80% of all systemic fungal infections and are the fourth leading cause of all nosocomial bloodstream infections in the United States.¹ The impact of fungal infections on health care and economic expenditures is large and of growing concern. Increases in infection rates are a consequence of growing numbers of at-risk subjects due to advances in transplantation technology and oncology treatment, spread of the Human Immunodeficiency Virus (HIV), use of vascular catheters, and extensive administration of broad-spectrum antibiotics.

In the United States, mortality rates in children with candidemia approach 30%, depending on the specific subject population and clinical setting.^{2,3} Current approved treatments for infections due to *Candida* spp. include polyenes, azoles and echinocandin antifungal agents. Of these, amphotericin B and fluconazole are the most commonly utilized in the paediatric population. Guidelines for use of these agents in the paediatric population have often been extrapolated from adult studies.

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 candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in adults. **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 patients with invasive *Candida* infection. This study will assess the pharmacokinetics, safety and efficacy of anidulafungin in patients 1 month to <18 years of age with ICC. Exposure-response relationships of anidulafungin will also be assessed in a population pharmacokinetic-pharmacodynamic (PK-PD) analysis.

Change To

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3. Section, PROTOCOL SUMMARY, Study Design

Change From

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)**~~ICC. The planned enrollment is 60 subjects over 16 months at approximately 20-40 sites.~~

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. (e.g., 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). In the latter case, culture confirmation of *Candida* sp. must be obtained within 96 hours post treatment initiation. If culture confirmation is not obtained within this time period, subjects will be discontinued from study treatment but will remain in the study for continued safety monitoring. These subjects will be required to return for the 2-week and 6-week follow-up visits.

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 10 days of IV treatment, provided that the pre-specified criteria are met.

It is expected that the majority of subjects will receive study drug in the hospital; subjects will be permitted to complete study medication on an outpatient basis if deemed appropriate by the investigator. All 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 ~~of~~ 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. This will be considered the End of Treatment (EOT). Total treatment duration with anidulafungin is not to exceed 35 days. Subjects will be followed in the study for a total of 6 weeks after EOT.

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine or serum pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated **every three days (i.e., on Days 3 and 7)** ~~and every third day thereafter~~ until two cultures separated by at least 24 hours are confirmed to be negative. Any negative blood culture after Day 1 (per protocol schedule or otherwise) must be repeated after 24 hours.

Anidulafungin pharmacokinetics will be assessed in the first 6 subjects aged between 1 month to <2 years, to be enrolled at selected centers. Use of a second systemic antifungal agent (eg, amphotericin B) will be permitted for these 6 subjects only. Three subjects in this cohort will be between 1 and <6 months of age and 3 subjects will be between 6 months and <2 years of age, which will be enrolled in parallel. Data from these 6 subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. The exposure data from these subjects will be used to confirm if the recommended dosing regimen is appropriate for subjects aged <2 years. After the PK data is evaluated and dosing regimen is confirmed, subjects between 1 month to <2 years of age will be permitted to be

enrolled at all sites. Subsequent to this time point, use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted.

A population PK-PD analysis will also be performed in all other subjects enrolled and will include subjects <2 years of age who are not part of the 6 subject cohort described above, in which 3 to 5 sparse pharmacokinetic samples will be collected.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure 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.

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

We plan to amend this protocol at a future time to allow for the enrollment of neonates (from 0 to 1 month of age) when additional pharmacokinetic data are available for this patient population.

Change To

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. (e.g., 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). In the latter case, culture confirmation of *Candida* sp. must be obtained within 96 hours post treatment initiation. If culture confirmation is not obtained within this time period, subjects will be discontinued from study treatment but will remain in the study for continued safety monitoring. These subjects will be required to return for the 2-week and 6-week follow-up visits.

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It is expected that the majority of subjects will receive study drug in the hospital; subjects will be permitted to complete study medication on an outpatient basis if deemed appropriate

by the investigator. All 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. This will be considered the End of Treatment (EOT). Total treatment duration with anidulafungin is not to exceed 35 days. Subjects will be followed in the study for a total of 6 weeks after EOT.

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

We plan to amend this protocol at a future time to allow for the enrollment of neonates (from 0 to 1 month of age) when additional pharmacokinetic data are available for this patient population.

4. Section, PROTOCOL SUMMARY, Objectives, Secondary, 4th bullet

Change From

- To assess rates of relapse (**recurrence**) at the Week 2 and Week 6 FU visits;

Change To

- To assess rates of relapse (recurrence) at the Week 2 and Week 6 FU visits;

5. Section, PROTOCOL SUMMARY, Endpoints, Secodnary, Endpoints, 4th bullet

Change From

- Rates of relapse (**recurrence**) at the Week 2 and Week 6 FU visits;

Change To

- Rates of relapse (recurrence) at the Week 2 and Week 6 FU visits;

6. Section, PROTOCOL SUMMARY, Statistical Methods, 2nd and 4th paragraphs

Change From

Secondary efficacy analyses will be assessed in the Modified Intent-to-Treat (MITT) population, defined as all subjects who have received at least one dose of study drug and who have microbiological **confirmation evidence** of *Candida* infection. The efficacy analysis will be an assessment of global response, conducted by frequencies and percentages of global response (success, failure).

Other analyses will include rates of relapse (**recurrence**) and new infection at FU visits, and analysis of time to death during study therapy and FU visits.

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7. Section, Schedule of Activities and Footnotes

Change From

	Screening ¹	Daily through EOT	Day 3	Day 7	Day 10	Days 11-34	End of IV Therapy	End of Oral Therapy (if applicable)	Follow-Up Visit (EOT + 2 weeks) (± 2 days)	Long term Follow-Up (EOT + 6 weeks) (± 1 week)
Informed consent	X	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-
Complete physical examination (including vital signs) ²	X									
Targeted physical examination (Including vital signs)			X	X	X	Every 3 days	X	X	X	X
Temperature	X	X							X	X
Signs and symptoms	X				X		X	X	X	X
Urine or serum	X ³						X ³	X ³		X ³
Dilated Fundoscopic exam ⁴	X ⁵						X ⁶⁴	X ⁶⁴	X ⁶	X ⁶
Blood cultures ⁷⁵	X ⁸		X	X	X	X	X	X	X ⁹	X ⁹
Specimen culture ¹⁰⁶	X ¹⁰	X ¹⁰					X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰
CBC with differential ¹¹⁷	X		X	X		Every 7 Days	X	X	X ¹²⁸	X ¹²⁸
Serum chemistry ¹¹	X		X	X		Every 7 Days	X	X	X ¹²⁸	X ¹²⁸
Pharmacokinetic sampling (first 6 subjects 1 month to <2 yrs old) ^{13,149,10}		Days 1 and 2								
Pharmacokinetic sampling (all other subjects) ¹⁵⁺⁺		Days 1, 3, 5, 7 and 9								
Study medication administration		X								
Adverse events		X							X	X

Concomitant medications	X ¹⁶	X							X ¹⁷	X ¹⁷
Evaluation of Clinical and Microbiologic Global Response							X	X	X	X
Follow up evaluation (relapse [recurrence], new infection, or continued resolution/improvement)									X	X

1. Screening procedures/assessments are to be completed before the first dose of study medication.
2. May occur within 72 hours before the first dose of study medication.
3. **A urine or serum pregnancy test will be performed at screening (prior to treatment initiation), at the** For females of childbearing potential. This ~~urine (or serum) pregnancy test is to be repeated at the end of therapy or at the end of IV therapy, IV or oral, whichever is later, and at the 6-week follow-up visit. Additional pregnancy testing may also be performed repeated as per request of the IRB/EC or as required by local regulations.~~
4. Fundoscopic exams should be performed with pupils dilated if possible. In addition, when required by the protocol, the exam should be performed by an ophthalmologist unless it is not possible for practical reasons, in which case it may be performed by a non-ophthalmologist.
5. If it is not possible to perform a fundoscopic examination prior to the first dose of study drug, it may be performed up to 48 hours after the first dose of study drug.
6. To be completed only if the baseline fundoscopic examination was abnormal.
7. ~~Screening blood culture is to be obtained within 96 hours before the first dose of Study Drug (Day 1). Blood cultures will be obtained at screening and repeated every three (3) days thereafter (i.e., on Day 3 and 7), and every three days until two (2) consecutive cultures, separated by at least 24 hours, are confirmed to be negative while on study medication. and as clinically indicated. Pathogen isolated will be documented.~~
8. **Screening blood culture is to be obtained within 96 hours before the first dose of Study Drug (Day 1). For the screening blood culture, it is preferable for two (2) aerobic blood cultures to be obtained from two (2) separate sites, however, if this is not practical for clinical reasons, the required screening blood cultures may be collected according to local practice standards and as the clinical circumstances dictate.**
9. **For subjects who are prematurely discontinued from treatment for any reason, a blood sample for culture should be obtained only if it is clinically indicated.**
10. Cultures of other sterile sites as clinically indicated. Pathogen isolated will be documented.

11. CBC with differential (including RBC count and platelets count), and serum chemistry tests (AST, ALT, Alk-Phos, total Bilirubin, Albumin, BUN, Cr, Bicarbonate, Glucose, Na, K, Ca, Cl, Mg) are to be repeated on Day 3, 7 and every seven days during treatment phase, and repeated at both follow-up visits.

12. Hematology and chemistry tests should be repeated at both follow-up visits.

13. Prior to the administration of the first dose of study drug, a plasma sample (0.1 – 0.2 mL) should be obtained. Excess blood collected for safety laboratory testing may be used for this sample, otherwise it should be collected directly from the subject. Following the initiation of study drug treatment Six blood samples (0.3 – 0.5 mL each) will be collected for anidulafungin measurement at the following time points in the first 6 subjects: on Day 1 (receiving 3.0 mg/kg IV infusion); 2 minutes before the end of infusion; on Day 2 (receiving 1.5 mg/kg IV infusion): just prior to the start of the infusion, 2 minutes before the end of infusion, and 6, 12 and 24 hours after the start of infusion. Exact sampling times may be modified to accommodate subject schedules provided the actual time of collection is documented in the Case Report Form (CRF).

14. For the first 6 subjects aged 1 month to <2 years, use of a second systemic antifungal agent (eg, amphotericin B) will be permitted (these subjects will be enrolled at selected centers).

15. Samples (0.3 – 0.5 mL) will be collected for anidulafungin measurement at 3-5 of the following occasions during the study: Day 1: Post-dose (between 0-2 hours following the end of anidulafungin infusion); Day 3: Pre-dose (just prior to the start of anidulafungin infusion); Day 5: Post-dose (between 0-3 hours following the end of anidulafungin infusion); Day 7: Delayed post-dose (between 6-12 hours following the end of anidulafungin infusion); Day 9: Pre-dose (just prior to the start of anidulafungin infusion). Exact sampling times may be modified to accommodate subject schedules as long as the samples are collected during the IV treatment period.

16. Only antifungal medications the subject has received within the past 30 days prior to enrolment are required to be recorded.

17. Only antifungal medications and their indication for use (e.g., for prophylaxis or treatment) are required to be reported during the follow-up period unless the subject experiences an adverse effect during this time, in which case all concomitant medications the subject was receiving at the time of the adverse event must be recorded.

Change To

	Screening ¹	Daily through EOT	Day 3	Day 7	Day 10	Days 11-34	End of IV Therapy	End of Oral Therapy (if applicable)	Follow-Up Visit (EOT + 2 weeks) (± 2 days)	Long term Follow-Up (EOT + 6 weeks) (± 1 week)
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Targeted physical examination (Including vital signs)			X	X	X	Every 3 days	X	X	X	X
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Signs and symptoms	X				X		X	X	X	X
Urine or serum pregnancy test ³	X ³						X ³	X ³		X ³
Dilated fundoscopic exam ⁴	X ⁵						X ⁶	X ⁶	X ⁶	X ⁶
Blood cultures ⁷	X ⁸		X	X			X	X	X ⁹	X ⁹
Specimen culture ¹⁰	X ¹⁰	X ¹⁰					X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰
CBC with differential ¹¹	X		X	X		Every 7	X	X	X ¹²	X ¹²
Serum chemistry ¹¹	X		X	X		Every 7	X	X	X ¹²	X ¹²
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Pharmacokinetic sampling (all other subjects) ¹⁵		Days 1, 3, 5, 7 and 9								
Study medication administration		X								

Adverse events		X							X	X
Concomitant medications	X ¹⁶	X							X ¹⁷	X ¹⁷
Evaluation of Clinical and Microbiologic Response							X	X	X	X
Follow up evaluation (relapse [recurrence], new infection, or continued resolution/ improvement)									X	X

1. Screening procedures/assessments are to be completed before the first dose of study medication.

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9. For subjects who are prematurely discontinued from treatment for any reason, a blood sample for culture should be obtained only if it is clinically indicated.

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11. CBC with differential (including RBC count and platelets count), and serum chemistry tests (AST, ALT, Alk-Phos, total Bilirubin, Albumin, BUN, Cr, Bicarbonate, Glucose, Na, K, Ca, Cl, Mg) are to be repeated on Day 3, 7 and every seven days during treatment phase, and repeated at both follow-up visits.

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16. Only antifungal medications the subject has received within the past 30 days prior to enrolment are required to be recorded.

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8. Section 1. INTRODUCTION, 3rd paragraph

Addition

On 14 November 2007, Health Canada approved IV anidulafungin for the treatment of invasive candidiasis/candidemia in adult non-neutropenic patients.

9. Section 1. INTRODUCTION, 1.2. Background and Rationale, 1st-3rd paragraphs

Change From

The incidence of systemic invasive fungal infections has risen significantly in the past decade. Infections due to *Candida* spp. account for about 80% of all systemic fungal infections and are the fourth leading cause of all nosocomial bloodstream infections in the United States.¹ The impact of fungal infections on health care and economic expenditures is large and of growing concern. Increases in infection rates are a consequence of growing numbers of at-risk patients due to advances in transplantation technology and oncology treatment, spread of the Human Immunodeficiency Virus (HIV), use of vascular catheters, and extensive administration of broad-spectrum antibiotics.

In the United States, mortality rates in children with candidemia approach 30%, depending on the specific patient population and clinical setting.^{2,3} Current approved treatments for infections due to *Candida* spp. include polyenes, azoles and echinocandin antifungal agents. Of these, amphotericin B and fluconazole are the most commonly utilized in the paediatric population. Guidelines for use of these agents in the paediatric population have often been extrapolated from adult studies.

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 candidemia 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.**

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The incidence of systemic invasive fungal infections has risen significantly in the past decade. Infections due to *Candida* spp. account for about 80% of all systemic fungal infections and are the fourth leading cause of all nosocomial bloodstream infections in the United States.¹ The impact of fungal infections on health care and economic expenditures is large and of growing concern. Increases in infection rates are a consequence of growing numbers of at-risk patients due to advances in transplantation technology and oncology treatment, spread of the Human Immunodeficiency Virus (HIV), use of vascular catheters, and extensive administration of broad-spectrum antibiotics.

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10. Section 1. INTRODUCTION, 1.3.2. Clinical Data, Clinical Pharmacy, 8th and 9th paragraphs

Change From

The safety of anidulafungin has been assessed in 929 subjects, including 672 subjects in Phase 2/3 studies. Treatment-related adverse events that were reported in $\geq 2\%$ of subjects in the pivotal Phase 3 comparative candidemia and other forms of invasive candidiasis study in adults included diarrhea, increased alkaline phosphatase and hypokalemia.⁴

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Anidulafungin Investigator Brochure.⁵

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Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Anidulafungin Investigator Brochure.⁵

11. Section 1. INTRODUCTION, 1.4. Overview of Fluconazole

Change From

~~1.4. Additional information can be found in the Investigator's Brochure and the approved physician prescribing information.~~ **Overview of Fluconazole**

Fluconazole is an azole antifungal agent used in the treatment of infection due to *Candida* sp. Information regarding the approved indications for fluconazole can be found in the manufacturer's approved product labeling. Complete information for this

compound may be found in the Single Reference Safety Document, which for this study is the Fluconazole Core Data Sheet.⁶

Change To

1.4. Overview of Fluconazole

Fluconazole is an azole antifungal agent used in the treatment of infection due to *Candida* sp. Information regarding the approved indications for fluconazole can be found in the manufacturer's approved product labeling. Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Fluconazole Core Data Sheet.⁶

12. Section 2. STUDY OBJECTIVES AND ENDPOINTS, 2.1. Objectives, Secondary, 4th bullet

Change From

- To assess rates of relapse (**recurrence**) at the Week 2 and Week 6 FU visits;

Change To

- To assess rates of relapse (recurrence) at the Week 2 and Week 6 FU visits;

13. Section 2. STUDY OBJECTIVES AND ENDPOINTS, 2.2. Endpoints, Secondary, 4th bullet

Change From

- Rates of relapse (**recurrence**) at the Week 2 and Week 6 FU visits

Change To

- Rates of relapse (recurrence) at the Week 2 and Week 6 FU visits

14. Section 3. STUDY DESIGN

Change From

This prospective, open-label, non-comparative study will assess the pharmacokinetics, 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**). ~~The planned enrollment is 60 subjects over 16 months at approximately 20-40 sites.~~

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). In the latter case, culture confirmation of *Candida* sp. must be obtained within 96 hours post treatment initiation. If culture confirmation is not obtained within this time period, subjects will be discontinued from study treatment but will remain in the study for continued safety monitoring. These subjects will be required to return for the 2-week and 6-week follow-up visits.

All subjects meeting screening criteria will receive IV anidulafungin. Enrollment will be stratified by age (1 month - <2 years, 2 - <5 years, and 5 - <18 years), allowing 20 ± 2 in each stratum. Subjects may be switched to oral fluconazole (6-12 mg/kg/day, maximum 800 mg/day) after at least 10 days of IV anidulafungin treatment, provided that all of the following criteria are met:

- The subject is afebrile for at least 24 hours;
- The subject is able to tolerate oral medication;
- Documentation of two blood cultures negative for *Candida* spp separated by at least 24 hours;
- Documentation of a negative culture for *Candida* spp from any other sites of infection identified at enrollment;
- The specific *Candida* isolate identified at study entry is susceptible to fluconazole;
- Signs and symptoms of *Candida* infection have improved such that the Investigator feels it is appropriate to switch to oral fluconazole.

It is expected that the majority of subjects will receive study drug in the hospital; subjects will be permitted to complete study medication on an outpatient basis if deemed appropriate by the investigator.

All subjects will receive treatment (either solely IV anidulafungin, or anidulafungin followed by oral fluconazole) for a minimum duration of 14 days from the time of the last of 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 symptoms of candidemia or invasive candidiasis. This will be considered the EOT. Total treatment duration with anidulafungin is not to exceed 35 days. Subjects will be followed in the study for a total of 6 weeks after EOT.

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine or serum pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated **every three days (ie, on Days 3 and 7)** ~~and every third day thereafter~~ until two cultures separated by at least 24 hours are confirmed

to be negative. If blood cultures are performed more frequently than required by the protocol; a second blood culture after 24 hours of any negative culture is required.

Anidulafungin pharmacokinetics will be assessed in the first 6 subjects aged between 1 month to <2 years, to be enrolled at selected centers. Use of a second systemic antifungal agent (eg, amphotericin B) will be permitted for these 6 subjects only. Three subjects in this cohort will be between 1 and <6 months of age and 3 subjects will be between 6 months and <2 years of age. Data from these 6 subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. The exposure data from these subjects will be used to confirm if the recommended dosing regimen is appropriate for subjects aged <2 years. After the dosing regimen is confirmed, subjects between 1 month to <2 years of age will be permitted to be enrolled at all sites. Subsequent to this time point, use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted.

A population PK-PD analysis will also be performed in all other subjects enrolled and will include subjects <2 years of age who are not part of the 6 subject cohort described above, in which 3 to 5 sparse pharmacokinetic samples will be collected.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure 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.

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

We plan to amend this protocol at a future time to allow for the enrollment of neonates (from 0 to 1 month of age) when additional pharmacokinetic data are available for this patient population.

Change To

This prospective, open-label, non-comparative study will assess the pharmacokinetics, 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). In the latter case, culture confirmation of *Candida* sp. must be obtained within 96 hours post treatment initiation. If culture confirmation is not obtained within this time period, subjects will be discontinued from study

treatment but will remain in the study for continued safety monitoring. These subjects will be required to return for the 2-week and 6-week follow-up visits.

All subjects meeting screening criteria will receive IV anidulafungin. Enrollment will be stratified by age (1 month - <2 years, 2 - <5 years, and 5 - <18 years), allowing 20 ± 2 in each stratum. Subjects may be switched to oral fluconazole (6-12 mg/kg/day, maximum 800 mg/day) after at least 10 days of IV anidulafungin treatment, provided that all of the following criteria are met:

- The subject is afebrile for at least 24 hours;
- The subject is able to tolerate oral medication;
- Documentation of two blood cultures negative for *Candida* spp separated by at least 24 hours;
- Documentation of a negative culture for *Candida* spp from any other sites of infection identified at enrollment;
- The specific *Candida* isolate identified at study entry is susceptible to fluconazole;
- Signs and symptoms of *Candida* infection have improved such that the Investigator feels it is appropriate to switch to oral fluconazole.

It is expected that the majority of subjects will receive study drug in the hospital; subjects will be permitted to complete study medication on an outpatient basis if deemed appropriate by the investigator.

All subjects will receive treatment (either solely IV anidulafungin, or anidulafungin followed by oral fluconazole) for a minimum duration of 14 days from the time of the last of 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 symptoms of candidemia or invasive candidiasis. This will be considered the EOT. Total treatment duration with anidulafungin is not to exceed 35 days. Subjects will be followed in the study for a total of 6 weeks after EOT.

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine or serum pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated every three days (ie, on Days 3 and 7) until two cultures separated by at least 24 hours are confirmed to be negative. If blood cultures are performed more frequently than required by the protocol; a second blood culture after 24 hours of any negative culture is required.

Anidulafungin pharmacokinetics will be assessed in the first 6 subjects aged between 1 month to <2 years, to be enrolled at selected centers. Use of a second systemic antifungal agent (eg, amphotericin B) will be permitted for these 6 subjects only. Three subjects in this cohort will be between 1 and <6 months of age and 3 subjects will be between 6 months and <2 years of age. Data from these 6 subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. The exposure data from these subjects will be used to confirm if the recommended dosing regimen is appropriate for subjects aged <2 years. After the dosing regimen is confirmed, subjects between 1 month to <2 years of age will be permitted to be enrolled at all sites. Subsequent to this time point, use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted.

A population PK-PD analysis will also be performed in all other subjects enrolled and will include subjects <2 years of age who are not part of the 6 subject cohort described above, in which 3 to 5 sparse pharmacokinetic samples will be collected.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure 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.

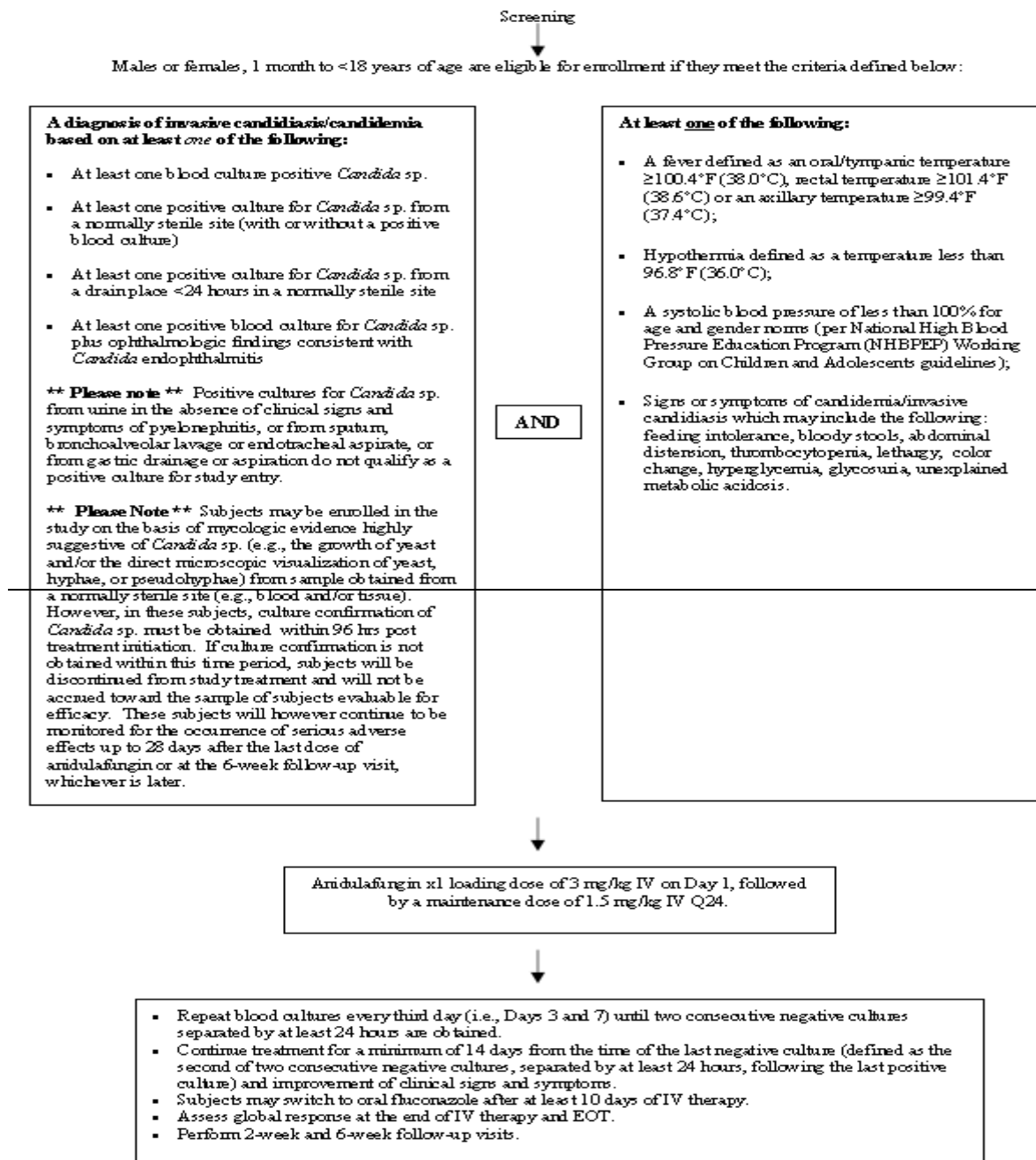
The planned enrolment is 60 evaluable subjects (those subjects who have received at least one dose and confirmed *Candida* infection).

We plan to amend this protocol at a future time to allow for the enrollment of neonates (from 0 to 1 month of age) when additional pharmacokinetic data are available for this patient population.

15. Section 3. STUDY DESIGN, Study Schematic

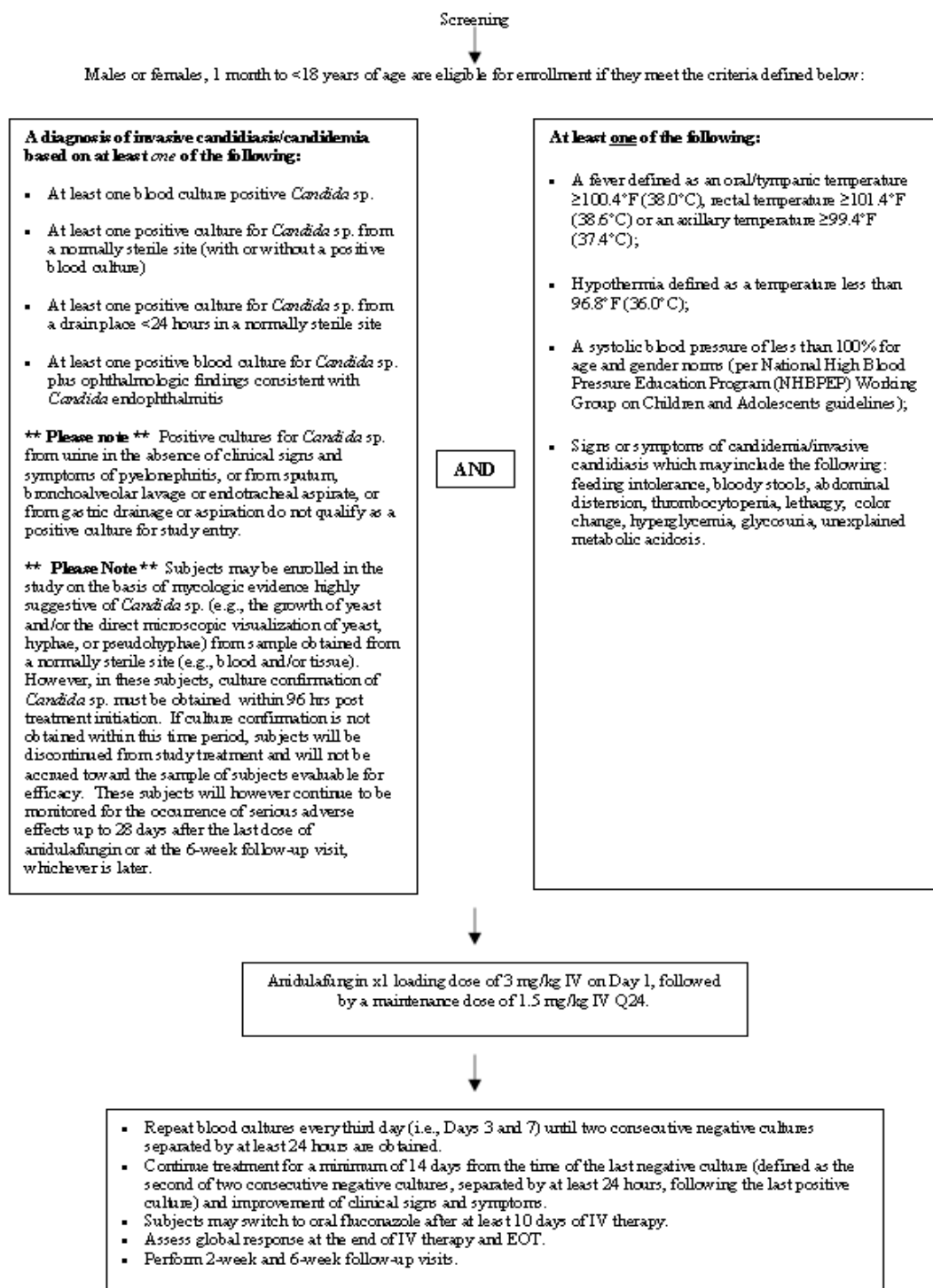
Change From

Study Schematic:



Study Schematic:

Change To



16. Section 4. SUBJECT SELECTION, 4.1. Inclusion Criteria

Change From

Subject eligibility should be reviewed and documented by an appropriate qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Diagnosis of **invasive candidiasis/candidemia (ICC) based on the growth of *Candida sp.*** from a blood **and/or tissue** culture **obtained from** ~~or a culture of a specimen from~~ a normally sterile site ~~taken~~ within 96 hours before study entry.

Diagnosis will be based on presence of at least one of the following:

- Candidemia: at least one blood culture positive for ~~yeast~~ ***Candida sp.*** (in the absence of other demonstrated foci of infection) or;
- Other forms of invasive candidiasis: positive culture for ***Candida sp.*** ~~yeast~~ from a specimen from a normally sterile site with or without a positive blood culture; positive ~~yeast~~ culture **for *Candida sp.*** from a ~~newly placed~~ drain **placed <24 hours** in a normally sterile site; ~~a or any~~ positive blood culture for ***Candida sp.*** ~~yeast~~ plus ophthalmic examination consistent with Candida endophthalmitis.

NOTE: Positive ~~yeast~~ cultures **for *Candida sp.*** from sputum (including those obtained by bronchoalveolar lavage or an endotracheal aspirate) will not qualify as a positive culture.

AND

At least one of the following:

- A fever defined as an oral/tympanic temperature $\geq 100.4^{\circ}\text{F}$ (38.0°C), rectal temperature $\geq 101.4^{\circ}\text{F}$ (38.6°C) or an axillary temperature $\geq 99.4^{\circ}\text{F}$ (37.4°C);
- Hypothermia defined as a temperature less than 96.8°F (36.0°C);
- A systolic blood pressure of less than 100% for age and gender norms (per National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents guidelines);⁷
- Signs or symptoms of candidemia/invasive candidiasis which may include the following: feeding intolerance, bloody stools, abdominal distension, thrombocytopenia, lethargy, color change, hyperglycemia, glycosuria, unexplained metabolic acidosis.

**** Important Notes ****

Subjects may be enrolled in the study on the basis of mycologic 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 (eg, blood and/or tissue). However, in these subjects, culture confirmation of *Candida* sp. must be obtained within 96 hours post treatment initiation. If culture confirmation is not obtained within this time period, subjects will be discontinued from study treatment but will remain in the study for continued safety monitoring. These subject will be required to return for the 2-week and 6-week follow-up visits.

Positive cultures for *Candida* sp. from urine (in the absence of clinical signs and symptoms of pyelonephritis), sputum, bronchoalveolar lavage (BAL), endotracheal aspiration, gastric drainage or gastric aspiration do not qualify as a positive culture for study entry.

2. Male or female between the ages of 1 month and <18 years. Females of childbearing potential must have adequate contraception as determined by the Investigator for the duration of the trial.
3. For each subject, parent or legal guardian must be willing and able to provide signed and dated written informed consent documentation. Assent from the child or adolescent will be obtained as appropriate. This is to be obtained prior to enrollment.
4. Will be available for the duration of the study and be able to abide by the study restrictions.

Change To

Subject eligibility should be reviewed and documented by an appropriate qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Diagnosis of invasive candidiasis/candidemia (ICC) based on the growth of *Candida* sp. from a blood and/or tissue culture obtained from a normally sterile site within 96 hours before study entry.

Diagnosis will be based on presence of at least one of the following:

- Candidemia: at least one blood culture positive for *Candida* sp. (in the absence of other demonstrated foci of infection) or;
- Other forms of invasive candidiasis: positive culture for *Candida* sp. from a specimen from a normally sterile site with or without a positive blood culture;

positive culture for *Candida* sp. from a drain placed <24 hours in a normally sterile site; a positive blood culture for *Candida* sp. plus ophthalmic examination consistent with *Candida* endophthalmitis.

NOTE: Positive cultures for *Candida* sp. from sputum (including those obtained by bronchoalveolar lavage or an endotracheal aspirate) will not qualify as a positive culture.

AND

At least one of the following:

- A fever defined as an oral/tympanic temperature $\geq 100.4^{\circ}\text{F}$ (38.0°C), rectal temperature $\geq 101.4^{\circ}\text{F}$ (38.6°C) or an axillary temperature $\geq 99.4^{\circ}\text{F}$ (37.4°C);
- Hypothermia defined as a temperature less than 96.8°F (36.0°C);
- A systolic blood pressure of less than 100% for age and gender norms (per National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents guidelines);⁷
- Signs or symptoms of candidemia/invasive candidiasis which may include the following: feeding intolerance, bloody stools, abdominal distension, thrombocytopenia, lethargy, color change, hyperglycemia, glycosuria, unexplained metabolic acidosis.

**** Important Notes ****

Subjects may be enrolled in the study on the basis of mycologic 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 (eg, blood and/or tissue). However, in these subjects, culture confirmation of *Candida* sp. must be obtained within 96 hours post treatment initiation. If culture confirmation is not obtained within this time period, subjects will be discontinued from study treatment but will remain in the study for continued safety monitoring. These subject will be required to return for the 2-week and 6-week follow-up visits.

Positive cultures for *Candida* sp. from urine (in the absence of clinical signs and symptoms of pyelonephritis), sputum, bronchoalveolar lavage (BAL), endotracheal aspiration, gastric drainage or gastric aspiration do not qualify as a positive culture for study entry.

2. Male or female between the ages of 1 month and <18 years. Females of childbearing potential must have adequate contraception as determined by the Investigator for the duration of the trial.
3. For each subject, parent or legal guardian must be willing and able to provide signed and dated written informed consent documentation. Assent from the child or adolescent will be obtained as appropriate. This is to be obtained prior to enrollment.

4. Will be available for the duration of the study and be able to abide by the study restrictions.

17. Section 4. SUBJECT SELECTION, 4.2. Exclusion Criteria, numbers 3, note under number 5 14, and last note

Change From

3. Known history of **intolerance**, allergy, hypersensitivity or serious reaction to **anidulafungin or any of its excipients (including fructose), or to other echinocandin antifungals.**

**** Important Note ** Prior antifungal prophylaxis is allowed.**

14. Subjects with a prosthetic devices **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 randomization (within 24 – 48 hours).** [~~Hemodialysis shunts (AV fistulae) may remain in situ).~~]

**** Please Note ** If it is anticipated that a prosthetic device or vascular catheter cannot be removed within this time frame, the medical monitor should be contacted to discuss enrolment.**

Change To

3. Known history of intolerance, allergy, hypersensitivity or serious reaction to anidulafungin or any of its excipients (including fructose), or to other echinocandin antifungals.

**** Important Note ** Prior antifungal prophylaxis is allowed.**

14. Subjects with 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 randomization (within 24 – 48 hours).

**** Please Note ** If it is anticipated that a prosthetic device or vascular catheter cannot be removed within this time frame, the medical monitor should be contacted to discuss enrolment.**

18. Section 5. STUDY TREATMENTS, 5.1. Allocation to Treatment, last paragraph

Change From

Treatment will continue 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

symptoms of candidemia or invasive candidiasis. This will be considered the EOT. Subject will be followed in the study for a total of 6 weeks after EOT.

Change To

Treatment will continue 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 symptoms of candidemia or invasive candidiasis. This will be considered the EOT. Subject will be followed in the study for a total of 6 weeks after EOT.

19. Section 5. STUDY TREATMENTS, 5.2.1. Formulation and Packaging

Change From

Study Drug

Generic Name: Anidulafungin
Trade Name: Eraxis™/Ecalta®
Dosage Form: Intravenous
Strength: 100 mg
Manufacturer: Pfizer Inc.

Clinical Supply

Packaging: Anidulafungin (Eraxis™/Ecalta®) for Injection will be supplied as an investigational product by the Pfizer Supply Chain. Anidulafungin for injection will be packaged and labeled to meet study-specific and regulatory requirements. Written Dosing Administration Instructions (DAI) will be provided that describe the method for reconstitution and further dilution of anidulafungin in preparation for administration.

Each participating site is responsible to provide the Water for Injection (WFI), USP in order to reconstitute the lyophilized anidulafungin. Each site is also responsible to provide the necessary intravenous solutions required to further dilute the reconstituted anidulafungin for administration by IV infusion. Refer to the Dosing Administration Instructions for detailed instructions on dose preparation.

Oral Medication

Generic Name: Fluconazole
Dosage Form: Oral tablets and oral suspension
Strength: Oral tablets containing 50, 100, 150, or 200 mg of fluconazole.

Oral Suspension containing ~~350 mg or 1400 mg~~ **10 mg/mL, 40 mg/mL or 50 mg/mL of fluconazole.**

Manufacturer: Pfizer Inc. **or generic manufacturer**

Clinical Supply

Packaging: Each participating site is responsible to procure commercially packaged fluconazole tablets and oral suspension as needed.

Note: If applicable, the site can use the locally available capsule formulation of fluconazole.

Change To

Study Drug

Generic Name: Anidulafungin

Trade Name: Eraxis™/Ecalta®

Dosage Form: Intravenous

Strength: 100 mg

Manufacturer: Pfizer Inc.

Clinical Supply

Packaging: Anidulafungin (Eraxis™/Ecalta®) for Injection will be supplied as an investigational product by the Pfizer Supply Chain. Anidulafungin for injection will be packaged and labeled to meet study-specific and regulatory requirements. Written Dosing Administration Instructions (DAI) will be provided that describe the method for reconstitution and further dilution of anidulafungin in preparation for administration.

Each participating site is responsible to provide the Water for Injection (WFI), USP in order to reconstitute the lyophilized anidulafungin. Each site is also responsible to provide the necessary intravenous solutions required to further dilute the reconstituted anidulafungin for administration by IV infusion. Refer to the Dosing Administration Instructions for detailed instructions on dose preparation.

Oral Medication

Generic Name: Fluconazole

Dosage Form: Oral tablets and oral suspension

Strength: Oral tablets containing 50, 100, 150, or 200 mg of fluconazole.

Oral Suspension containing 10 mg/mL, 40 mg/mL or 50 mg/mL of fluconazole.

Manufacturer: Pfizer Inc. or generic manufacturer

Clinical Supply

Packaging: Each participating site is responsible to procure commercially packaged fluconazole tablets and oral suspension as needed.

Note: If applicable, the site can use the locally available capsule formulation of fluconazole.

20. Section 5. STUDY TREATMENTS, 5.4. Concomitant Medication(s), 1st-3rd paragraphs

Change From

Any medication that the subject takes other than the study drug specified in the protocol is considered concomitant medication. Information about concomitant medications will be recorded in the Case Report Form (CRF) from the screening visit through the EOT. ~~In addition, any antifungal treatments used between EOT and 6-week FU visit will be documented.~~

At the 2-week and 6-week FU Visits, only antifungal therapy the subject receives and the indication for use (eg, prophylaxis, treatment) will be recorded in the CRF. The use of non-absorbable antifungal drugs (eg, clotrimazole troches) is not required to be reported.

The recording of concomitant medications other than antifungal agents at these time points is not required unless the subject experiences an adverse event during the follow-up period, in which case all concomitant medications that the subject was receiving at the time of the adverse event must be recorded.

Change To

Any medication that the subject takes other than the study drug specified in the protocol is considered concomitant medication. Information about concomitant medications will be recorded in the Case Report Form (CRF) from the screening visit through the EOT.

At the 2-week and 6-week FU Visits, only antifungal therapy the subject receives and the indication for use (eg, prophylaxis, treatment) will be recorded in the CRF. The use of non-absorbable antifungal drugs (eg, clotrimazole troches) is not required to be reported.

The recording of concomitant medications other than antifungal agents at these time points is not required unless the subject experiences an adverse event during the follow-up period, in which case all concomitant medications that the subject was receiving at the time of the adverse event must be recorded.

21. Section 6. STUDY PROCEDURES, 6.1. Screening Visit, 1st paragraph, 2nd, 3rd, 8th bullets

Change From

The following screening activities should occur following the informed consent and within two days **prior to** ~~of the~~ first dose.

- Medical, surgical, and medication history (Please note: only antifungal medications that the subject was receiving within the past 30 days prior to enrolment are required to be recorded);
- Fundoscopic examination (Please Note: Fundoscopic examination should be performed with eyes dilated if possible. In addition, if it is not possible to perform a fundoscopic examination prior to the first dose of study drug, it may be performed up to 48 hours after the first dose);

Change To

The following screening activities should occur following the informed consent and within two days prior to first dose.

- Medical, surgical, and medication history (Please note: only antifungal medications that the subject was receiving within the past 30 days prior to enrolment are required to be recorded);
- Fundoscopic examination (Please Note: Fundoscopic examination should be performed with eyes dilated if possible. In addition, if it is not possible to perform a fundoscopic examination prior to the first dose of study drug, it may be performed up to 48 hours after the first dose);

22. Section 6. STUDY PROCEDURES, 6.2.2. Days 1 and 2 ONLY for Sub-study Subjects (first 6 subjects aged 1 month to <2 years at selected sites), 1st paragraph and 1st bullet

Change From

Prior to the administration of the first dose of study drug, a plasma sample (0.1 – 0.2 mL) should be obtained and sent to the reference laboratory to test for assay interference. Excess blood collected for safety laboratory testing may be used for this sample, otherwise it should be collected directly from the subject.

- Pharmacokinetic sampling: Six blood samples (0.3-0.5 ml each **to provide 0.1 – 0.2 mL plasma**) will be collected for anidulafungin measurement at the following time points:

Change To

Prior to the administration of the first dose of study drug, a plasma sample (0.1 – 0.2 mL) should be obtained and sent to the reference laboratory to test for assay interference. Excess blood collected for safety laboratory testing may be used for this sample, otherwise it should be collected directly from the subject.

- Pharmacokinetic sampling: Six blood samples (0.3-0.5 ml each to provide 0.1 – 0.2 mL plasma) will be collected for anidulafungin measurement at the following time points:

23. Section 6. STUDY PROCEDURES, 6.2.6. Day 10, last paragraph

Deletion

~~Blood cultures:~~

24. Section 6. STUDY PROCEDURES, 6.2.7. Days 11 to 34 (day prior to last day of IV anidulafungin therapy – maximum is 35 days on anidulafungin), 2nd bullet

Deletion

- Blood cultures → to continue to be repeated every 3 days until two cultures separated by at least 24 hours are confirmed to be negative;

25. Section 6. STUDY PROCEDURES, 6.3. End of IV Anidulafungin Therapy, 8th, 9th bullets

Change From

- Evaluation of **clinical and microbiologic** ~~Global~~ Response (See Section 7.2);
- Urine or serum pregnancy test (for females of childbearing potential) to be done at the End of Treatment ~~p~~Period **in subjects who are not switched to oral therapy.**

Change To

- Evaluation of clinical and microbiologic Response (See Section 7.2);
- Urine or serum pregnancy test (for females of childbearing potential) to be done at the End of Treatment period in subjects who are not switched to oral therapy.

26. Section 6. STUDY PROCEDURES, 6.4. End of Oral Therapy (if applicable), 8th 9th bullets

Change From

- Urine or serum pregnancy test (for females of childbearing potential);

- Evaluation of **clinical and microbiologic** ~~rGlobal~~ Response (See Section 0).

Change To

- Urine or serum pregnancy test (for females of childbearing potential);
- Evaluation of clinical and microbiologic response (See Section 0).

27. Section 6. STUDY PROCEDURES, 6.5. Follow Up Visit (End of Treatment + 2 weeks), 9th bullet

Change From

- Evaluation of **clinical and microbiologic** ~~rGlobal~~ Response (See Section 0);

Change To

- Evaluation of clinical and microbiologic response (See Section 0);

28. Section 6. STUDY PROCEDURES, 6.6. Long Term Follow-Up (End of Treatment + 6 weeks), 10th bullet

Change From

- Evaluation of **clinical and microbiologic** ~~rGlobal~~ Response (See Section 0);

Change To

- Evaluation of clinical and microbiologic response (See Section 0);

29. Section 6. STUDY PROCEDURES, 6.7. Subject Withdrawal

Change From

Subjects may withdraw from the study **treatment** at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. **If a subject is withdrawn from the study treatment, on the last day of study drug administration the investigator will perform all EOT procedures and complete the EOT CRF.**

In addition, these subjects will continue to be monitored for the occurrence of adverse effects (serious and non-serious) for up to 6 weeks after the last dose of study treatment, and are required to return to clinic for the 2-week and 6-week follow-up visits, at which time only the following activities will be performed:

- A brief physical exam;
- Record vital signs (including temperature);

- Obtain blood for culture (only if clinically indicated);
- Obtain non-blood specimen from normally sterile site for culture (only if clinically indicated);
- Obtain blood for hematology and chemistry panel;
- Record adverse events since the last study visit;
- Record the use of systemic antifungal medications since the last study visit; if the subject experienced an adverse event, record all concomitant medications the subject was receiving at the time of the adverse event.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. ~~The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.~~

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Change To

Subjects may withdraw from the study treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject is withdrawn from the study treatment, on the last day of study drug administration the investigator will perform all EOT procedures and complete the EOT CRF.

In addition, these subjects will continue to be monitored for the occurrence of adverse effects (serious and non-serious) for up to 6 weeks after the last dose of study treatment, and are required to return to clinic for the 2-week and 6-week follow-up visits, at which time only the following activities will be performed:

- A brief physical exam;
- Record vital signs (including temperature);
- Obtain blood for culture (only if clinically indicated);
- Obtain non-blood specimen from normally sterile site for culture (only if clinically indicated);
- Obtain blood for hematology and chemistry panel;

- Record adverse events since the last study visit;
- Record the use of systemic antifungal medications since the last study visit; if the subject experienced an adverse event, record all concomitant medications the subject was receiving at the time of the adverse event.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

30. Section 6. STUDY PROCEDURES, 6.8. Subject Withdrawal Due to Lack of Confirmation of Candida Infection

Addition

6.8. Subject Withdrawal Due to Lack of Confirmation of Candida Infection

Subjects who were enrolled on the basis of suspected *Candida* infection will be discontinued from the study treatment if culture results are either negative for *Candida* sp. or not obtained within 96 hours after treatment initiation, and treated as clinically warranted. If a subject is withdrawn from study treatment, on the last day of study drug administration the investigator will perform all EOT procedures and complete the EOT CRF.

In addition, these subjects will continue to be monitored for the occurrence of adverse effects (serious and non-serious) for up to 6 weeks after the last dose of study treatment and are required to return to clinic for the 2-week and 6-week follow-up visits, at which time only the following activities will be performed:

- A brief physical exam;
- Record vital signs (including temperature);
- Obtain blood for culture (only if clinically indicated);
- Obtain non-blood specimen from normally sterile site for culture (only if clinically indicated);
- Obtain blood for hematology and chemistry panel;
- Record adverse events since the last study visit;

- Record the use of systemic antifungal medications since the last study visit; if the subject experienced an adverse event, record all concomitant medications the subject was receiving at the time of the adverse event.

31. Section 6. STUDY PROCEDURES, 6.9. Discontinuation Criteria for Abnormal Liver Function Tests

Addition

6.9. Discontinuation Criteria for Abnormal Liver Function Tests

It is important for investigators to monitor carefully for any adverse events, including elevations of liver function tests that could be related to anidulafungin.

Subjects who experience an increase in AST, ALT or total bilirubin that exceeds either one of the two thresholds outlined below, at any time during the study, must be discontinued from treatment with anidulafungin.

- AST and/or ALT >3x the upper limit of normal AND total bilirubin >1.5x the upper limit of normal, and no evidence of biliary obstruction (eg, elevated alkaline phosphatase in the context of gallbladder disease, bile duct disease or malignancy) or other explanation (eg, viral hepatitis, autoimmune hepatitis);
- AST and/or ALT >10x the upper limit of normal, regardless of causality.

Note: These subjects will be discontinued from study treatment but will remain in the study for safety monitoring according to the procedures described in section 6.7.

32. Section 6. STUDY PROCEDURES, 6.10. Discontinuation Criteria for Persistent Candidemia

Addition

6.10. Discontinuation Criteria for Persistent Candidemia

Subjects who were either candidemic at baseline or become candidemic during the course of the study will be considered treatment failures and discontinued from study treatment if candidemia persists for more than 7 days.

Note: These subjects will be discontinued from study treatment but will remain in the study for safety monitoring according to the procedures described in section 6.7.

33. Section 7. ASSESSMENTS, 2nd paragraph

Addition

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may

be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test can not be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

34. Section 7. ASSESSMENTS, 7.1. Clinical Assessments, letter c, and 2nd, 3rd paragraphs

Change From

c. Medical History: including (as appropriate) age, gender, medical history, surgical history, prior medications (**only antifungal agents within 30 days prior to enrolment**), adverse reactions to medications, and history of hepatic, renal, or cardiovascular systems.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure at the EOIVT, EOT and FU visits. Rates of relapse (**recurrence**) and/or new infection will be assessed at the FU visits. **These efficacy parameters will be derived in the analysis from the investigator's assessment of clinical and microbiologic response, and are defined below.** ~~These efficacy parameters are defined below.~~

Global response, which ~~will be derived from~~ ~~incorporates both~~ **investigator assessed** clinical and microbiologic responses, will be ~~defined~~ ~~categorized~~ as follows:

Change To

c. Medical History: including (as appropriate) age, gender, medical history, surgical history, prior medications (only antifungal agents within 30 days prior to enrolment), adverse reactions to medications, and history of hepatic, renal, or cardiovascular systems.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure at the EOIVT, EOT and FU visits. Rates of relapse (recurrence) and/or new infection will be assessed at the FU visits. These efficacy parameters will be derived in the analysis from the investigator's assessment of clinical and microbiologic response, and are defined below.

Global response, which will be derived from both investigator assessed clinical and microbiologic responses, will be defined as follows:

35. Section 7. ASSESSMENTS, 7.1. Clinical Assessments, Microbiological Response, letter a

Change From

- a. Relapse (**recurrence**): Any baseline *Candida* spp 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;

Change To

- a. **Relapse (recurrence)**: Any baseline *Candida* spp 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;

36. Section 7. ASSESSMENTS, 7.3. Fundoscopic Examinations

Addition

7.3. Fundoscopic Examinations

Fundoscopy exams should be performed with pupils dilated if possible. In addition, when required by the protocol, the exam should be performed by an ophthalmologist unless it is not possible for practical reasons, in which case it may be performed by a non-ophthalmologist.

37. Section 7. ASSESSMENTS, 7.5.3. Microbiological Determinations, numbers 1 ,2, letters a

Change From

1. Screening Blood Cultures: A screening blood culture will be obtained within 96 hours before the first dose of Study Drug (Day 1). For the screening blood culture, it is preferable for two (2) aerobic blood cultures to be obtained from two (2) separate sites, however, if this is not practical for clinical reasons, the required screening blood cultures may be collected according to local practice standards and as the clinical circumstances dictate. ~~Two (2) aerobic blood cultures from 2 different sites will be performed at screening on all subjects.~~ If the screening positive baseline culture was drawn > 96 hours before the start of treatment, the blood cultures should be repeated. If the screening blood samples for culture were taken <96 hours before study entry, blood cultures do not need to be repeated. Peripheral venipuncture is the preferred method for obtaining blood cultures.

2. ~~Screening Baseline c~~**Cultures for specimens** (other than blood): Obtained as clinically indicated.

- a. Blood cultures will be obtained at screening and every three (3) days thereafter (i.e., on Day 3 and 7) until two (2) consecutive cultures, separated by at least 24 hours, are confirmed to be negative while on study medication, ~~Blood cultures will be repeated on Days 3, 7, 10 and every third day thereafter until two cultures~~

~~separated by at least 24 hours are confirmed to be negative while on study medication,~~ at the end of IV therapy, end of oral therapy, and at the early and late follow-up visits. Additional cultures may be obtained at the investigator's discretion as clinically indicated.

Change To

1. Screening Blood Cultures: A screening blood culture will be obtained within 96 hours before the first dose of Study Drug (Day 1). For the screening blood culture, it is preferable for two (2) aerobic blood cultures to be obtained from two (2) separate sites, however, if this is not practical for clinical reasons, the required screening blood cultures may be collected according to local practice standards and as the clinical circumstances dictate. If the screening positive baseline culture was drawn > 96 hours before the start of treatment, the blood cultures should be repeated. If the screening blood samples for culture were taken <96 hours before study entry, blood cultures do not need to be repeated. Peripheral venipuncture is the preferred method for obtaining blood cultures.

2. Screening cultures for specimens other than blood: Obtained as clinically indicated.

a. Blood cultures will be obtained at screening and every three (3) days thereafter (ie, on Day 3 and 7) until two (2) consecutive cultures, separated by at least 24 hours, are confirmed to be negative while on study medication, at the end of IV therapy, end of oral therapy, and at the early and late follow-up visits. Additional cultures may be obtained at the investigator's discretion as clinically indicated.

38. Section 7. ASSESSMENTS, 7.6.1. Blood Sampling for Subjects in the PK Sub-Study (1 month to <2 years of age)

Change From

7.6.2. Blood Sampling for Subjects in the PK Sub-Study (1 month to <2 years of age)

~~Plasma for analysis of anidulafungin.~~

~~The first 6 children aged <2 years enrolled in the PK substudy (to be enrolled at selected centers) will undergo the PK sampling as described below.~~

Prior to the administration of the first dose of study drug, a plasma sample (0.1 – 0.2 mL) should be obtained and sent to the reference laboratory to test for assay interference. Excess blood collected for safety laboratory testing may be used for this sample, otherwise it should be collected directly from the subject.

Following initiation of treatment, blood samples (approximately 0.3 - 0.5 mL each) will be collected for anidulafungin measurement at the following 6 time points.

On Day 1 (receiving 3 mg/kg IV infusion): 2 minutes before the end of infusion;

On Day 2 (receiving 1.5 mg/kg IV infusion): just prior to the start of infusion, 2 minutes before the end of infusion, 6, 12 and 24 hours after the start of infusion.

Due to the special conditions of the study population, the sampling time and day can be flexible in order to fit the subject's schedule. For instance, if serial pharmacokinetic sampling cannot be scheduled on Day 2, subjects will continue to remain on IV treatment to allow sample collection at a later date. The actual sampling time and date will be recorded in the CRF.

~~In addition, in order to ensure there is no assay interference in these 6 subjects, it is recommended to send a blank plasma sample (0.1 – 0.2 mL) from these subjects to the assay laboratory for potential interference check. This small amount may be left from the Screening safety lab test if available; otherwise it should be collected.~~

Change To

7.6.1. Blood Sampling for Subjects in the PK Sub-Study (1 month to <2 years of age)

The first 6 children aged <2 years enrolled in the PK substudy (at selected centers) will undergo the PK sampling as described below.

Prior to the administration of the first dose of study drug, a plasma sample (0.1 – 0.2 mL) should be obtained and sent to the reference laboratory to test for assay interference. Excess blood collected for safety laboratory testing may be used for this sample, otherwise it should be collected directly from the subject.

Following initiation of treatment, blood samples (approximately 0.3 - 0.5 mL each) will be collected for anidulafungin measurement at the following 6 time points.

- On Day 1 (receiving 3 mg/kg IV infusion): 2 minutes before the end of infusion;
- On Day 2 (receiving 1.5 mg/kg IV infusion): just prior to the start of infusion, 2 minutes before the end of infusion, 6, 12 and 24 hours after the start of infusion.

Due to the special conditions of the study population, the sampling time and day can be flexible in order to fit the subject's schedule. For instance, if serial pharmacokinetic sampling cannot be scheduled on Day 2, subjects will continue to remain on IV treatment to allow sample collection at a later date. The actual sampling time and date will be recorded in the CRF.

39. Section 7. ASSESSMENTS, 7.6.2. Blood Sampling for All Subjects (Except for the First Six Subjects Age 1 Month to <2 Yrs Enrolled in the PK Sub-Study), Title, After 4th paragraph of section, 7.6.1. Blood Sampling for Subjects in the PK Sub-Study (1 month to < 2 years of age), Title 7.6.2. Blood Sampling for All Subjects (Except for the First Six Subjects Age 1 Month to <2 Yrs Enrolled in the PK Sub-Study), added

Addition

7.6.2. Blood Sampling for All Subjects (Except for the First Six Subjects Age 1 Month to <2 Yrs Enrolled in the PK Sub-Study)

40. Section 8. ADVERSE EVENT REPORTING, 8.2. Reporting Period, 1st paragraph

Change From

For serious adverse events, the reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product **or at the 6-week follow-up visit, whichever is later.** Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected;

Change To

For serious adverse events, the reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product or at the 6-week follow-up visit, whichever is later. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected;

41. Section 9. DATA ANALYSIS/STATISTICAL METHODS, 9.2. Analysis of Secondary Endpoints, 1st and 3rd paragraphs

Change From

The efficacy analysis will be an assessment of global response at EOIVT, EOT, 2 week and 6 week FU visits. **Global response will be derived from the investigator's assessment of clinical and microbiological response as defined in Section 7.1.** The analysis will be conducted by frequencies and percentages of global response by determination (success, failure). These efficacy analyses will be assessed in the Modified Intent-to-Treat (MITT) population, which will be defined as all subjects who have received at least one dose of study drug and who have microbiological **confirmation evidence** of *Candida* infection.

Rates of relapse (recurrence) and new infection at FU visits will also be derived from the investigator's assessment of clinical and microbiologic response as defined in Section 7.1, and analyzed. Time to death will be analyzed and all-cause mortality rates determined. ~~Other analyses will include rates of relapse and new infection at FU visits, and analysis of time to death to determine all-cause mortality rates.~~

Change To

The efficacy analysis will be an assessment of global response at EOIVT, EOT, 2 week and 6 week FU visits. Global response will be derived from the investigator's assessment of clinical and microbiological response as defined in Section 7.1. The analysis will be conducted by frequencies and percentages of global response by determination (success, failure). These efficacy analyses will be assessed in the Modified Intent-to-Treat (MITT) population, which will be defined as all subjects who have received at least one dose of study drug and who have microbiological confirmation of *Candida* infection.

Rates of relapse (recurrence) and new infection at FU visits will also be derived from the investigator's assessment of clinical and microbiologic response as defined in Section 7.1, and analyzed. Time to death will be analyzed and all-cause mortality rates determined.

42. Section 9. DATA ANALYSIS/STATISTICAL METHODS, 9.4. Sample Size Determination

Change From

Since this is a descriptive study, sample size calculations were not performed. A sample size of 60 **evaluable** subjects for this study was chosen based on the number of subjects estimated to be necessary to provide adequate information for assessing **efficacy**, safety and tolerability in children with ICC. **Evaluable subjects are those that have received at least one dose of study medication and have a confirmed *Candida* infection.**

Change To

Since this is a descriptive study, sample size calculations were not performed. A sample size of 60 evaluable subjects for this study was chosen based on the number of subjects estimated to be necessary to provide adequate information for assessing efficacy, safety and tolerability in children with ICC. Evaluable subjects are those that have received at least one dose of study medication and have a confirmed *Candida* infection.

43. Section 9. DATA ANALYSIS/STATISTICAL METHODS, 9.7. Data Monitoring Committee, title and section

Addition

9.7. Data Monitoring Committee

This study will use an Independent Data Monitoring Committee (IDMC).

44. Section 11. DATA HANDLING AND RECORD KEEPING, 11.1. 3rd paragraph

Change From

The investigator has ultimate responsibility for the **collection and reporting accuracy, authenticity, and timely collection and reporting** of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms **(source documents) and ensuring that**

they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

Change To

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

45. Section 11. DATA HANDLING AND RECORD KEEPING, 11.2. Record Retention, 2nd paragraph

Change From

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to **an independent third party arranged by Pfizer**. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

Change To

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

46. Section 12. ETHICS, 12.2. Ethical Conduct of the Study, 1st paragraph

Change From

The study will be conducted in accordance with **legal and regulatory requirements, as well as the general principles set forth in the international ethical guidelines for biomedical research involving human subjects (Counsel for International Organization of Medical Science 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association**

~~2008). on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996).~~

Change To

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the international ethical guidelines for biomedical research involving human subjects (Counsel for International Organization of Medical Science 2002), Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008).

47. Section 15. PUBLICATION OF STUDY RESULTS, 4th paragraph

Change From

The study results synopsis posted on ClinicalStudyResults.org (called the PhRMA website synopsis) uses the format established by the ICH-E3 Clinical Study Report (CSR) Synopsis. Study results will be posted ~~If posting of study results to ClinicalStudyResults.org within one year of last subject last visit. For all studies subject to FDA Amendments Act Title VIII and the state of Maine disclosure legislation, Pfizer also posts data in the basic results database on ClinicalTrials.gov within 1 year of the primary outcome completion date.~~ jeopardizes a planned publication of the study results, a Pending Full Publication notice is substituted for the synopsis until the study results publication has issued or two years have elapsed, whichever occurs first.

Change To

The study results synopsis posted on ClinicalStudyResults.org (called the PhRMA website synopsis) uses the format established by the ICH-E3 Clinical Study Report (CSR) Synopsis. Study results will be posted to ClinicalStudyResults.org within one year of last subject last visit. For all studies subject to FDA Amendments Act Title VIII and the state of Maine disclosure legislation, Pfizer also posts data in the basic results database on ClinicalTrials.gov within 1 year of the primary outcome completion date.

48. Section 16. REFERENCES, numbers 5,6,

Addition

5. Anidulafungin Investigator Brochure. May 2009.
6. Fluconazole Core Data Sheet. September 2009.

Appendix 4. CLINICAL PROTOCOL AMENDMENT 4

Current Amendment: 4

Amendment No.	Date	Country (ies)	Site(s)
4	19 August 2010		

Previous Amendments:

Amendment No.	Date	Country (ies)	Site(s)
3	21 September 2009		

Amendment No.	Date	Country (ies)	Site(s)
2	02 July 2008		

Amendment No.	Date	Country (ies)	Site(s)
1	07 December 2007		

SUMMARY

Reason(s) for Amendment

The primary reasons for creation of this protocol amendment are as follows:

- To remove the exclusion criteria and allow for the enrollment of subjects with *Candida* endocarditis on the basis of at least one positive blood culture for *Candida* sp. and evidence of endocarditis on echocardiogram;
- To remove the exclusion criteria and allow for the enrollment of subjects with *Candida* osteomyelitis on the basis of at least one positive culture for *Candida* sp. from a bone biopsy or aspirate and evidence of osteomyelitis on a magnetic resonance imaging (MRI) study;

The Sponsor has also taken the opportunity to make additions, changes, and clarifications to the protocol, as appropriate. Following is a summary of additional clarifications/modifications made:

- Clarified that subjects in the pharmacokinetics subgroup (ie, the first 6 subjects between 1 month and <2 years of age enrolled at selected centers) may be given anidulafungin as either monotherapy or in combination with a second antifungal therapy, at the investigator's discretion. In the event the investigator chooses to treat with combination therapy, then, following completion of PK sampling, these subjects will be discontinued from study treatment but will continue to be followed for safety assessments and are required to return for the 2- and 6-week follow-up visit.

- Clarified that the maximum total duration of treatment in this study is 49 days, and the maximum allowed treatment duration with anidulafungin is 35 days.
- Modified oral fluconazole switch criteria: In addition to other criteria currently listed in the protocol, allow switch to occur if microbiologic eradication is presumed based on clinical signs and symptoms, and if susceptibility to fluconazole is presumed based on the *Candida* species identified and based on local *Candida* sp. resistance patterns;
- Clarified that subjects may now have at least one clinical criteria present either at the time of study entry or within 96 hours prior to study entry.

Additional minor changes have also been made to the protocol. A complete listing of the protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

The protocol section(s) that have been amended and the details of the changes are summarized in the following sections.

Protocol Section(s) Amended

The protocol sections that were amended are detailed below. The format is as follows:

The “change from” section represents the current text in the protocol. Bolded text is used to indicate the addition of information to the current text, and strike-out of text (eg, ~~text~~) is used to show the deletion of information from the current text.

The “change to” section represents the revised text, with the revisions shown in the “change from” section in normal text.

Section <Insert section number> , <Insert section title> , Page
<Insert page number as appropriate>

Change From

Change To

1. Section, PROTOCOL SUMMARY, Study Design, 6th, 7th, and 9 through 11th paragraphs

Change From

The maximum total treatment duration in this study is 49 days, and the maximum allowed treatment duration with anidulafungin is 35 days. After at least 10 days of treatment with anidulafungin, subjects may be switched to oral fluconazole (provided switch criteria are met) to complete 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.

~~Total treatment duration with anidulafungin is not to exceed 35 days. Subjects will be followed in the study for a total of 6 weeks after EOT.~~

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. These subjects may be administered anidulafugin in one of two ways: either as monotherapy or in combination with a second systemic antifungal agent (e.g., amphotericin B).

In the event the investigator choses to administer anidulafungin as monotherapy for the treatment of invasive candidiasis/candidemia, treatment will be administered 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.

In the event the investigator chooses to administer anidulafungin in combination with a second antifungal agent, anidulafugin will be discontinued following the obtainment of required blood samples for pharmacokinetic analysis as specified by the protocol; the data from these subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. After the dosing regimen is confirmed by the Sponsor, enrollment will be opened to additional subjects within this age group at all investigator sites. Subsequent to this time point, the use of a second systemic antifungal agent (e.g., amphotericin B) will not be permitted in any subject.

~~Anidulafungin pharmacokinetics will be assessed in the first 6 subjects aged between 1 month to <2 years, to be enrolled at selected centers. Use of a second systemic antifungal agent (eg, amphotericin B) will be permitted for these 6 subjects only. Three subjects in this cohort will be between 1 and <6 months of age and 3 subjects will be between 6 months and <2 years of age, which will be enrolled in parallel. Data from these 6 subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. The exposure data from these subjects will be used to confirm if the recommended dosing regimen is appropriate for subjects aged <2 years. After the PK data is evaluated and dosing regimen is confirmed, subjects between 1 month to <2 years of age will be permitted to be enrolled at all sites. Subsequent to this time point, use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted.~~

Change To

The maximum total treatment duration in this study is 49 days, and the maximum allowed treatment duration with anidulafungin is 35 days. After at least 10 days of treatment with anidulafungin, subjects may be switched to oral fluconazole (provided switch criteria are met) to complete 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. These subjects may be administered anidulafugun in one of two ways: either as monotherapy or in combination with a second systemic antifungal agent (e.g., amphotericin B).

In the event the investigator chooses to administer anidulafungin as monotherapy for the treatment of invasive candidiasis/candidemia, treatment will be administered 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.

In the event the investigator chooses to administer anidulafungin in combination with a second antifungal agent, anidulafugun will be discontinued following the obtainment of required blood samples for pharmacokinetic analysis as specified by the protocol; the data from these subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. After the dosing regimen is confirmed by the Sponsor, enrollment will be opened to additional subjects within this age group at all investigator sites. Subsequent to

this time point, the use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted in any subject.

2. Section, PROTOCOL SUMMARY, Statistical Methods, 3rd paragraph

Deletion

~~Supportive analyses of the efficacy endpoint of global response will be performed in the Intent to Treat (ITT) population, consisting of all randomized subjects.~~

3. Schedule of Activities

Change From

Schedule of Activities

	Screening ¹	Daily through EOT	Day 3	Day 7	Day 10	Days 11-34	End of IV Therapy	End of Oral Therapy (if applicable)	Follow-Up Visit (EOT + 2 weeks) (± 2 days)	Long term Follow-Up (EOT + 6 weeks) (± 1 week)
Informed consent	X	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-
Complete physical examination (including vital signs) ²	X									
Targeted physical examination (Including vital signs)			X	X	X	Every 3 days ³	X	X	X	X
Temperature	X	X ³							X	X
Signs and symptoms assessment	X				X		X	X	X	X
Urine or serum pregnancy test ⁴³	X ⁴³						X ⁴³	X ⁴³		X ⁴³
Dilated fundoscopic exam ⁵⁴	X ⁶⁵						X ⁷⁶	X ⁷⁶	X ⁷⁶	X ⁷⁶
Blood cultures ⁸⁷	X ⁹⁸		X	X			X	X	X ¹⁰⁹	X ¹⁰⁹
Specimen culture ¹¹¹⁰	X ¹¹¹⁰	X ¹¹¹⁰					X ¹¹¹⁰	X ¹¹¹⁰	X ¹¹¹⁰	X ¹¹¹⁰
CBC with differential ¹²¹¹	X		X	X		Every 7 Days	X	X	X ¹³¹²	X ¹³¹²
Serum chemistry ¹²¹¹	X		X	X		Every 7 Days	X	X	X ¹³¹²	X ¹³¹²
Echocardiogram (only for subjects with <i>Candida</i> endocarditis)	X ¹⁴						X ¹⁵	X ¹⁵		
Magnetic Resonance Imaging (MRI) study (only for subjects with <i>Candida</i> osteomyelitis)	X ¹⁶						X ¹⁷	X ¹⁷		

Pharmacokinetic sampling (first 6 subjects 1 month to <2 weeks) ^{1813,1914}		Days 1 and 2								
Pharmacokinetic sampling (all other subjects) ²⁰¹⁵		Days 1, 3, 5, 7 and 9								
Study medication administration		X								
Adverse events		X						X		X
Concomitant medications	X ²¹¹⁶	X						X ²²¹⁷		X ²²¹⁷
Evaluation of Clinical and Microbiologic Response						X	X	X		X
Follow up evaluation (relapse [recurrence], new infection, or continued resolution/								X		X

1. Screening procedures/assessments are to be completed before the first dose of study medication.

2. May occur within 72 hours before the first dose of study medication.

3. Subjects undergoing treatment in the outpatient setting may have less frequent assessments, but not less than once every 7 days. Close monitoring of subjects in the outpatient setting is required.

4. A urine or serum pregnancy test will be performed at screening (prior to treatment initiation), at the end of therapy or at the end of IV therapy, whichever is later, and at the 6-week follow-up visit. Additional testing may also be performed as per request of the IRB/EC or as required by local regulations.

5. Fundoscopic exams should be performed with pupils dilated if possible. In addition, when required by the protocol, the exam should be performed by an ophthalmologist unless it is not possible for practical reasons, in which case it may be performed by **the principle investigator or subinvestigator. a non-ophthalmologist.**

6. If it is not possible to perform a **baseline** fundoscopic examination prior to the first dose of study drug, it may be performed up to 48 hours after the first dose. ~~of study drug~~**Under extenuating circumstances, if the fundoscopic examination cannot be performed prior to first dose or within 48 hours, every effort should be made to perform the examination as soon as possible thereafter. Please note, if the baseline fundoscopic examination is positive for findings consistent with Candida endophthalmitis, then a repeat fundoscopic examination is required at the end of treatment and at the 2- and 6-week follow-up visits. Additional fundoscopic assessments, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional fundoscopic examinations are performed, the results should be recorded on the case report form.**

7. To be completed only if the baseline fundoscopic examination was abnormal.

8. Blood cultures will be obtained **on Day 1 at screening** and every three (3) days thereafter (ie, on Day 3 and 7) until two (2) consecutive cultures, separated by at least 24 hours, are confirmed to be negative while on study medication. Pathogen isolated will be documented.

9. The ‘screening visit culture’ is the culture result that qualifies the subject for study entry (along with other inclusion criteria) and is from a blood or tissue sample that was obtained within 96 hours prior to the screening visit, that is positive for *Candida* sp. The result of this culture will be recorded on the ‘screening visit’ case report form. In the event the culture result from this sample is pending, plan to record the culture result on the screening visit case report form once the organism has been identified and the information is available. Please note, if the day of the screening visit is also Day 1 of treatment, a sample of blood for culture will be obtained; otherwise a sample of blood for culture is not required until the first day of treatment (Day 1), just prior to administration of study drug. Screening blood culture is to be obtained within 96 hours before the first dose of Study Drug (Day 1). For the screening blood culture, it is preferable for two (2) aerobic blood cultures to be obtained from two (2) separate sites, however, if this is not practical for clinical reasons, the required screening blood cultures may be collected according to local practice standards and as the clinical circumstances dictate.

10. For subjects who are prematurely discontinued from treatment for any reason, a blood sample for culture should be obtained only if it is clinically indicated.

11. Cultures of other sterile sites as clinically indicated. Pathogen isolated will be documented.

12. CBC with differential (including RBC count, **reticulocytes, white blood cells, neutrophils, lymphocytes, monocytes, basophils**, and platelets count), and serum chemistry tests (AST, ALT, Alk-Phos, total Bilirubin, Albumin, BUN **or Urea**, Cr, Bicarbonate, Glucose, Na, K, Ca, Cl, Mg) are to be repeated on Day 3, 7 and every seven days during treatment phase, and repeated at both follow-up visits.

13. Hematology and chemistry tests should be repeated at both follow-up visits.

14. An echocardiogram at the time of screening is not required if the test was already performed within the previous 96 hours (of the screening visit). The results of the echocardiogram, however, must be recorded in the case report form.

15. For subjects with *Candida* endocarditis, either a transesophageal (preferred) or transthoracic echocardiogram must be performed at the end of study treatment (ie, at the end of treatment with IV anidulafungin, or at the end of treatment with oral fluconazole in subjects who are switched to oral therapy). Additional echocardiogram assessments, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional echocardiogram assessments are performed, the results should be recorded on the case report form.

16. A magnetic resonance imaging (MRI) study at the time of screening is not required if the test was already performed within the previous 96 hours (of the screening visit). The results of the MRI, however, must be recorded in the case report form.

17. For subjects with *Candida* osteomyelitis, a magnetic resonance imaging (MRI) study of the affected area must be performed at the end of study treatment (i.e., at the end of treatment with IV anidulafungin, or at the end of treatment with oral fluconazole in subjects who are switched to oral therapy). Additional MRI studies, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional MRI studies are performed, the results should be recorded on the case report form.

18. Prior to the administration of the first dose of study drug, a plasma sample (0.1 – 0.2 mL) should be obtained. Excess blood collected for safety laboratory testing

may be used for this sample, otherwise it should be collected directly from the subject. Following the initiation of study drug treatment six blood samples (0.3 – 0.5 mL each) will be collected for anidulafungin measurement at the following time points in the first 6 subjects: on Day 1 (receiving 3.0 mg/kg IV infusion); 2 minutes before the end of infusion; on Day 2 (receiving 1.5 mg/kg IV infusion): just prior to the start of the infusion, 2 minutes before the end of infusion, and 6, 12 and 24 hours after the start of infusion. Exact sampling times may be modified to accommodate subject schedules provided the actual time of collection is documented in the Case Report Form (CRF).

19. For the first 6 subjects aged 1 month to <2 years, use of a second systemic antifungal agent (eg, amphotericin B) will be permitted (these subjects will be enrolled at selected centers).

20. Samples (0.3 – 0.5 mL) will be collected for anidulafungin measurement at 3-5 of the following occasions during the study: Day 1: Post-dose (between 0-2 hours following the end of anidulafungin infusion); Day 3: Pre-dose (just prior to the start of anidulafungin infusion); Day 5: Post-dose (between 0-3 hours following the end of anidulafungin infusion); Day 7: Delayed post-dose (between 6-12 hours following the end of anidulafungin infusion); Day 9: Pre-dose (just prior to the start of anidulafungin infusion). Exact sampling times may be modified to accommodate subject schedules as long as the samples are collected during the IV treatment period.

21. Only antifungal medications the subject has received within the past 30 days prior to enrolment are required to be recorded.

22. Only antifungal medications and their indication for use (eg, for prophylaxis or treatment) are required to be reported during the follow-up period unless the subject experiences an adverse effect during this time, in which case all concomitant medications the subject was receiving at the time of the adverse event must be recorded.

Change To

Schedule of Activities

	Screening ¹	Daily through EOT	Day 3	Day 7	Day 10	Days 11-34	End of IV Therapy	End of Oral Therapy (if applicable)	Follow-Up Visit (EOT + 2 weeks) (± 2 days)	Long term Follow-Up (EOT + 6 weeks) (± 1 week)
Informed consent	X	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-
Complete physical examination (including vital signs) ²	X									
Targeted physical examination (Including vital signs)			X	X	X	Every 3 days ³	X	X	X	X
Temperature	X	X ³							X	X
Signs and symptoms assessment	X				X		X	X	X	X
Urine or serum pregnancy test ⁴	X ⁴						X ⁴	X ⁴		X ⁴
Dilated fundoscopic exam ⁵	X ⁶						X ⁷	X ⁷	X ⁷	X ⁷
Blood cultures ⁸	X ⁹		X	X			X	X	X ¹⁰	X ¹⁰
Specimen culture ¹¹	X ¹¹	X ¹¹					X ¹¹	X ¹¹	X ¹¹	X ¹¹
CBC with differential ¹²	X		X	X		Every 7 Days	X	X	X ¹³	X ¹³
Serum chemistry ¹²	X		X	X		Every 7 Days	X	X	X ¹³	X ¹³
Echocardiogram (only for subjects with <i>Candida</i> endocarditis)	X ¹⁴						X ¹⁵	X ¹⁵		
Magnetic Resonance Imaging (MRI) study (only for subjects with <i>Candida</i> osteomyelitis)	X ¹⁶						X ¹⁷	X ¹⁷		

Pharmacokinetic sampling (first 6 subjects 1 month to <2)		Days 1 and 2								
Pharmacokinetic sampling (all other subjects) ²⁰		Days 1, 3, 5, 7 and 9								
Study medication administration		X								
Adverse events		X							X	X
Concomitant medications	X ²¹	X							X ²²	X ²²
Evaluation of Clinical and Microbiologic Response							X	X	X	X
Follow up evaluation (relapse [recurrence], new infection, or continued resolution/									X	X

1. Screening procedures/assessments are to be completed before the first dose of study medication.

2. May occur within 72 hours before the first dose of study medication.

3. Subjects undergoing treatment in the outpatient setting may have less frequent assessments, but not less than once every 7 days. Close monitoring of subjects in the outpatient setting is required.

4. A urine or serum pregnancy test will be performed at screening (prior to treatment initiation), at the end of therapy or at the end of IV therapy, whichever is later, and at the 6-week follow-up visit. Additional testing may also be performed as per request of the IRB/EC or as required by local regulations.

5. Fundoscopic exams should be performed with pupils dilated if possible. In addition, when required by the protocol, the exam should be performed by an ophthalmologist unless it is not possible for practical reasons, in which case it may be performed by the principle investigator or subinvestigator.

6. If it is not possible to perform a baseline fundoscopic examination prior to the first dose of study drug, it may be performed up to 48 hours after the first dose. Under extenuating circumstances, if the fundoscopic examination cannot be performed prior to first dose or within 48 hours, every effort should be made to perform the examination as soon as possible thereafter. Please note, if the baseline fundoscopic examination is positive for findings consistent with Candida endophthalmitis, then a repeat fundoscopic examination is required at the end of treatment and at the 2- and 6-week follow-up visits. Additional fundoscopic assessments, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional fundoscopic examinations are performed, the results should be recorded on the case report form.

7. To be completed only if the baseline fundoscopic examination was abnormal.

8. Blood cultures will be obtained on Day 1 and every three (3) days thereafter (ie, on Day 3 and 7) until two (2) consecutive cultures, separated by at least 24 hours, are confirmed to be negative while on study medication. Pathogen isolated will be documented.
9. The 'screening visit culture' is the culture result that qualifies the subject for study entry (along with other inclusion criteria) and is from a blood or tissue sample that was obtained within 96 hours prior to the screening visit, that is positive for *Candida* sp. The result of this culture will be recorded on the 'screening visit' case report form. In the event the culture result from this sample is pending, plan to record the culture result on the screening visit case report form once the organism has been identified and the information is available. Please note, if the day of the screening visit is also Day 1 of treatment, a sample of blood for culture will be obtained; otherwise a sample of blood for culture is not required until the first day of treatment (Day 1), just prior to administration of study drug.
10. For subjects who are prematurely discontinued from treatment for any reason, a blood sample for culture should be obtained only if it is clinically indicated.
11. Cultures of other sterile sites as clinically indicated. Pathogen isolated will be documented.
12. CBC with differential (including RBC count, reticulocytes, white blood cells, neutrophils, lymphocytes, monocytes, basophils, and platelet count), and serum chemistry tests (AST, ALT, Alk-Phos, total Bilirubin, Albumin, BUN or Urea, Cr, Bicarbonate, Glucose, Na, K, Ca, Cl, Mg) are to be repeated on Day 3, 7 and every seven days during treatment phase, and repeated at both follow-up visits.
13. Hematology and chemistry tests should be repeated at both follow-up visits.
14. An echocardiogram at the time of screening is not required if the test was already performed within the previous 96 hours (of the screening visit). The results of the echocardiogram, however, must be recorded in the case report form.
15. For subjects with *Candida* endocarditis, either a transesophageal (preferred) or transthoracic echocardiogram must be performed at the end of study treatment (ie, at the end of treatment with IV anidulafungin, or at the end of treatment with oral fluconazole in subjects who are switched to oral therapy). Additional echocardiogram assessments, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional echocardiogram assessments are performed, the results should be recorded on the case report form.
16. A magnetic resonance imaging (MRI) study at the time of screening is not required if the test was already performed within the previous 96 hours (of the screening visit). The results of the MRI, however, must be recorded in the case report form.
17. For subjects with *Candida* osteomyelitis, a magnetic resonance imaging (MRI) study of the affected area must be performed at the end of study treatment (ie, at the end of treatment with IV anidulafungin, or at the end of treatment with oral fluconazole in subjects who are switched to oral therapy). Additional MRI studies, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional MRI studies are performed, the results should be recorded on the case report form.
18. Prior to the administration of the first dose of study drug, a plasma sample (0.1 – 0.2 mL) should be obtained. Excess blood collected for safety laboratory testing may be used for this sample, otherwise it should be collected directly from the subject. Following the initiation of study drug treatment six blood samples (0.3 – 0.5 mL each) will be collected for anidulafungin measurement at the following time points in the first 6 subjects: on Day 1 (receiving 3.0 mg/kg IV infusion); 2 minutes before the end of infusion; on Day 2 (receiving 1.5 mg/kg IV infusion): just prior to the start of the infusion, 2 minutes before the end of infusion, and 6, 12 and 24 hours after the start of infusion. Exact sampling times may be modified to accommodate subject schedules provided the actual time of collection is

documented in the Case Report Form (CRF).

19. For the first 6 subjects aged 1 month to <2 years, use of a second systemic antifungal agent (eg, amphotericin B) will be permitted (these subjects will be enrolled at selected centers).

20. Samples (0.3 – 0.5 mL) will be collected for anidulafungin measurement at 3-5 of the following occasions during the study: Day 1: Post-dose (between 0-2 hours following the end of anidulafungin infusion); Day 3: Pre-dose (just prior to the start of anidulafungin infusion); Day 5: Post-dose (between 0-3 hours following the end of anidulafungin infusion); Day 7: Delayed post-dose (between 6-12 hours following the end of anidulafungin infusion); Day 9: Pre-dose (just prior to the start of anidulafungin infusion). Exact sampling times may be modified to accommodate subject schedules as long as the samples are collected during the IV treatment period.

21. Only antifungal medications the subject has received within the past 30 days prior to enrolment are required to be recorded.

22. Only antifungal medications and their indication for use (eg, for prophylaxis or treatment) are required to be reported during the follow-up period unless the subject experiences an adverse effect during this time, in which case all concomitant medications the subject was receiving at the time of the adverse event must be recorded.

4. Section 3 STUDY DESIGN, beginning with 4th bullet

Change From

- **Eradication** ~~Documentation of a negative culture for *Candida* sp.~~ **eradication of *Candida* sp.** ~~p~~-from any other sites of infection identified at enrollment;
- The specific *Candida* isolate identified at study entry is susceptible (or presumed to be susceptible based on the species identified and local *Candida* sp. resistance patterns) to fluconazole;
- Signs and symptoms of *Candida* infection have improved such that the Investigator feels it is appropriate to switch to oral fluconazole.

It is expected that the majority of subjects will receive study drug in the hospital; subjects will be permitted to complete study medication on an outpatient basis if deemed appropriate by the investigator.

All subjects will receive treatment (either solely IV anidulafungin, or anidulafungin followed by oral fluconazole) for a minimum duration of 14 days from the time of the last of 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 symptoms of candidemia or invasive candidiasis. This will be considered the EOT.

The maximum total treatment duration in this study is 49 days, and the maximum allowed treatment duration with anidulafungin is 35 days. After at least 10 days of treatment with anidulafungin, subjects may be switched to oral fluconazole (provided switch criteria are met) to complete 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.

~~Total treatment duration with anidulafungin is not to exceed 35 days.~~ **All Subjects enrolled in the study who receive at least one dose of study drug treatment, including those subjects who are discontinued from treatment (regardless of the reason), will be followed in the study for a total of 6 weeks after EOT (ie, the last dose of study drug treatment) and are required to return for the 2-week and 6-week follow-up visit.**

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine or serum pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated every three days (ie, on Days 3 and 7) until two cultures separated by at least 24 hours are confirmed to be negative. If blood cultures are performed more frequently than required by the protocol; a second blood culture after 24 hours of any negative culture is required.

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. These subjects may be administered anidulafungin in one of two ways: either as monotherapy or in combination with a second systemic antifungal agent (eg, amphotericin B).

If the investigator chooses to administer anidulafungin as monotherapy for the treatment of invasive candidiasis/candidemia, then treatment will be administered 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.

In the event the investigator chooses to administer anidulafungin in combination with a second antifungal agent, anidulafungin will be discontinued following the obtainment of required blood samples for pharmacokinetic analysis as specified by the protocol; the data from these subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. After the dosing regimen is confirmed by the Sponsor, enrollment will be opened to additional subjects within this age group at all investigator sites. Subsequent to this time point, the use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted in any subject.

~~Anidulafungin pharmacokinetics will be assessed in the first 6 subjects aged between 1 month to <2 years, to be enrolled at selected centers. Use of a second systemic antifungal agent (eg, amphotericin B) will be permitted for these 6 subjects only. Three subjects in this cohort will be between 1 and <6 months of age and 3 subjects will be between 6 months and <2 years of age. Data from these 6 subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. The exposure data from these subjects will be used to confirm if the recommended dosing regimen is appropriate for subjects aged <2 years. After the dosing regimen is confirmed, subjects between 1 month to <2 years of age will be permitted to be enrolled at all sites. Subsequent to this time point, use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted.~~

A population PK-PD analysis will also be performed in all other subjects enrolled and will include subjects <2 years of age who are not part of the 6 subject cohort described above, in which 3 to 5 sparse pharmacokinetic samples will be collected.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure 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.

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

We plan to amend this protocol at a future time to allow for the enrollment of neonates (from 0 to 1 month of age) when additional pharmacokinetic data are available for this patient population.

Study Schematic:

1st Schematic is Addition

2nd Schematic is Deletion

Screening



Males or females, 1 month to <18 years of age are eligible for enrollment if they meet the criteria defined below:

A diagnosis of invasive candidiasis/candidemia based on at least one of the following:

- At least one blood culture positive *Candida* sp.
- At least one positive culture for *Candida* sp. from a normally sterile site (with or without a positive blood culture)
- At least one positive culture for *Candida* sp. from a drain place <24 hours in a normally sterile site
- At least one positive blood culture for *Candida* sp. plus ophthalmologic findings consistent with *Candida* endophthalmitis
- *Candida* endocarditis: at least one positive culture for *Candida* sp. and evidence of endocarditis on echocardiogram
- *Candida* osteomyelitis: at least one positive culture for *Candida* sp. from a bone biopsy or aspirate and evidence of osteomyelitis on a magnetic resonance imaging (MRI) study

**** Please note **** Positive cultures for *Candida* sp. from urine in the absence of clinical signs and symptoms of pyelonephritis, or from sputum, bronchoalveolar lavage or endotracheal aspirate, or from gastric drainage or aspiration do not qualify as a positive culture for study entry.

**** Please Note **** Subjects may be enrolled in the study on the basis of mycologic evidence highly suggestive of *Candida* sp. (e.g., the growth of yeast and/or the direct microscopic visualization of yeast, hyphae, or pseudohyphae) from sample obtained from a normally sterile site (e.g., blood and/or tissue). However, in these subjects, culture confirmation of *Candida* sp. must be obtained within 96 hrs post treatment initiation. If culture confirmation is not obtained within this time period, subjects will be discontinued from study treatment and will not be accrued toward the sample of subjects evaluable for efficacy. These subjects will however continue to be monitored for the occurrence of serious adverse effects up to 28 days after the last dose of anidulafungin or at the 6-week follow-up visit, whichever is later.

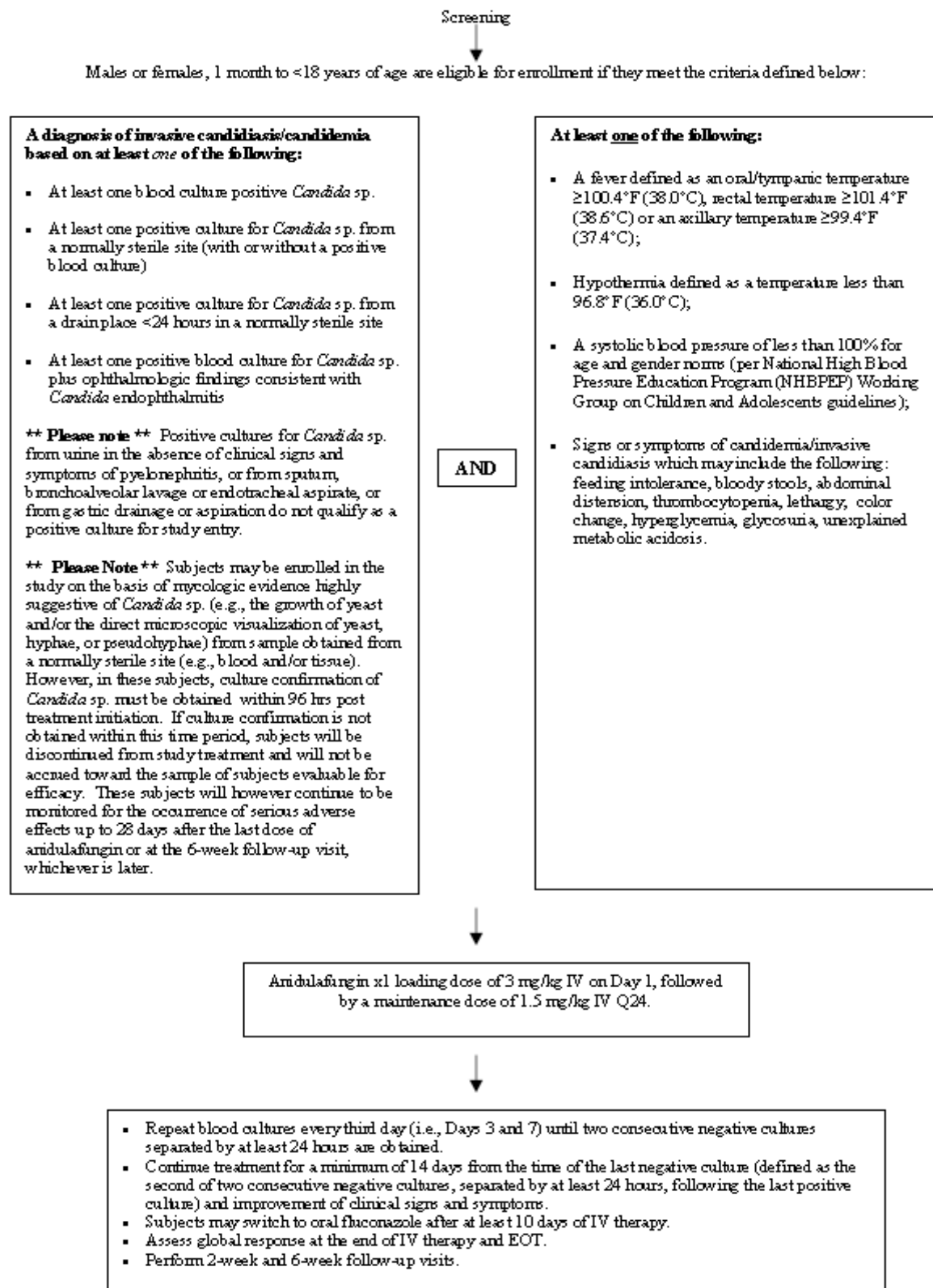
AND

At least one of the following:

- A fever defined as an oral/tympanic temperature $\geq 100.4^{\circ}\text{F}$ (38.0°C), rectal temperature $\geq 101.4^{\circ}\text{F}$ (38.6°C) or an axillary temperature $\geq 99.4^{\circ}\text{F}$ (37.4°C);
- Hypothermia defined as a temperature less than 96.8°F (36.0°C);
- A systolic blood pressure of less than 100% for age and gender norms (per National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents guidelines);
- Signs or symptoms of candidemia/invasive candidiasis which may include the following: feeding intolerance, bloody stools, abdominal distension, thrombocytopenia, lethargy, color change, hyperglycemia, glycosuria, unexplained metabolic acidosis.

Anidulafungin x1 loading dose of 3 mg/kg IV on Day 1, followed by a maintenance dose of 1.5 mg/kg IV Q24.

- Repeat blood cultures every third day (i.e., Days 3 and 7) until two consecutive negative cultures separated by at least 24 hours are obtained.
- Continue treatment for a minimum 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 symptoms.
- Subjects may switch to oral fluconazole after at least 10 days of IV therapy.
- Assess global response at the end of IV therapy and EOT.
- Perform 2-week and 6-week follow-up visits.



Change To

- Eradication or presumed eradication of *Candida* sp. from any other sites of infection identified at enrollment;
- The specific *Candida* isolate identified at study entry is susceptible (or presumed to be susceptible based on the species identified and local *Candida* sp. resistance patterns) to fluconazole;
- Signs and symptoms of *Candida* infection have improved such that the Investigator feels it is appropriate to switch to oral fluconazole.

It is expected that the majority of subjects will receive study drug in the hospital; subjects will be permitted to complete study medication on an outpatient basis if deemed appropriate by the investigator.

All subjects will receive treatment (either solely IV anidulafungin, or anidulafungin followed by oral fluconazole) for a minimum duration of 14 days from the time of the last of 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 symptoms of candidemia or invasive candidiasis. This will be considered the EOT.

The maximum total treatment duration in this study is 49 days, and the maximum allowed treatment duration with anidulafungin is 35 days. After at least 10 days of treatment with anidulafungin, subjects may be switched to oral fluconazole (provided switch criteria are met) to complete 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.

All subjects enrolled in the study who receive at least one dose of study drug treatment, including those subjects who are discontinued from treatment (regardless of the reason), will be followed for a total of 6 weeks after EOT (ie, the last dose of study drug treatment) and are required to return for the 2-week and 6-week follow-up visit.

All subjects will have the following assessments at the screening visit: physical examination, assessment of signs and symptoms of *Candida* infection, urine or serum pregnancy test (for females of childbearing potential), fundoscopic examination, blood cultures, specimen culture or histopathology of other normally sterile sites (as clinically indicated), and safety laboratory testing. Blood cultures will be repeated every three days (ie, on Days 3 and 7) until two cultures separated by at least 24 hours are confirmed to be negative. If blood

cultures are performed more frequently than required by the protocol; a second blood culture after 24 hours of any negative culture is required.

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. These subjects may be administered anidulafungin in one of two ways: either as monotherapy or in combination with a second systemic antifungal agent (eg, amphotericin B).

If the investigator chooses to administer anidulafungin as monotherapy for the treatment of invasive candidiasis/candidemia, then treatment will be administered 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.

In the event the investigator chooses to administer anidulafungin in combination with a second antifungal agent, anidulafungin will be discontinued following the obtainment of required blood samples for pharmacokinetic analysis as specified by the protocol; the data from these subjects will not be utilized for secondary efficacy endpoint analyses but will be assessed for safety. After the dosing regimen is confirmed by the Sponsor, enrollment will be opened to additional subjects within this age group at all investigator sites. Subsequent to this time point, the use of a second systemic antifungal agent (eg, amphotericin B) will not be permitted in any subject.

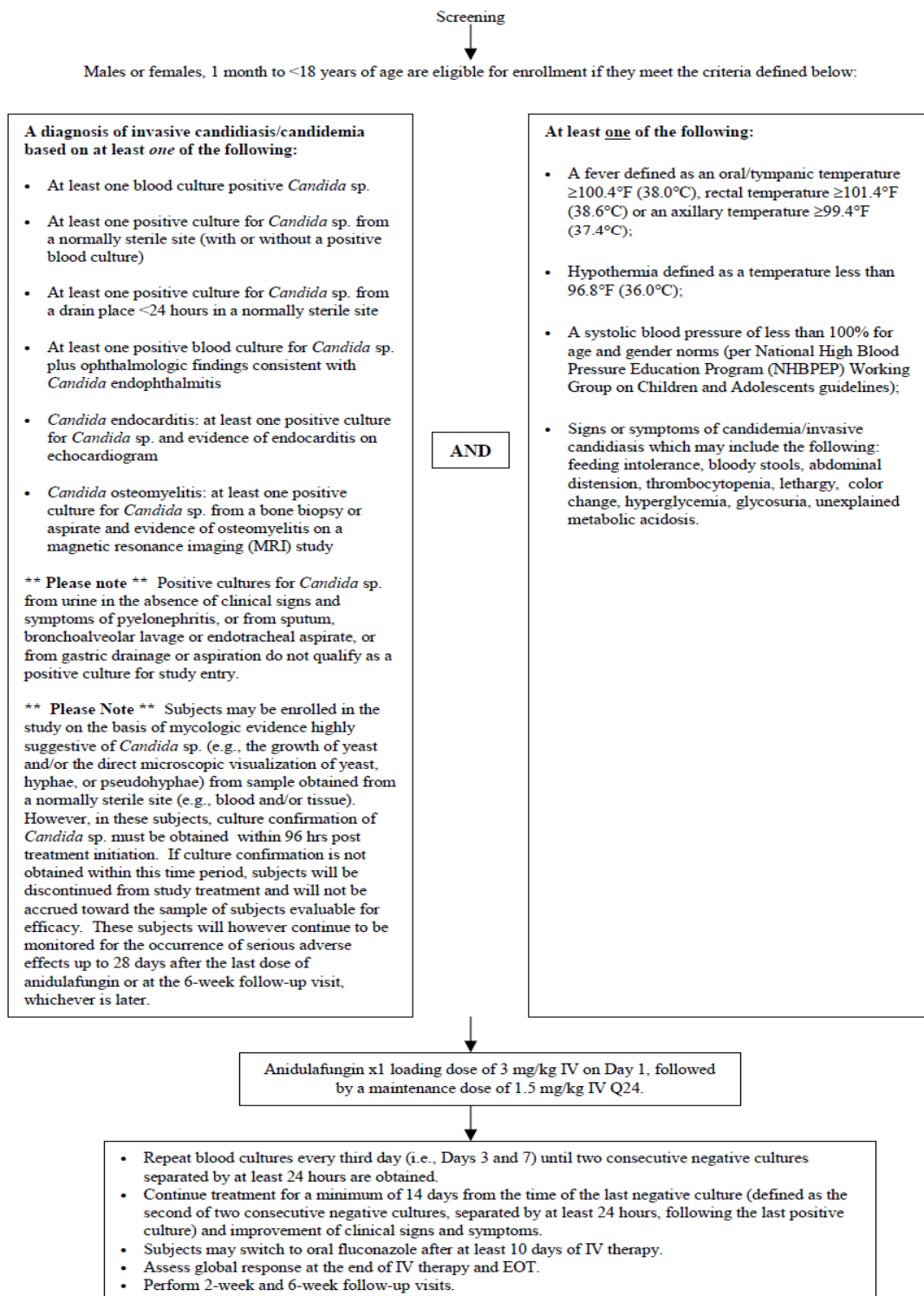
A population PK-PD analysis will also be performed in all other subjects enrolled and will include subjects <2 years of age who are not part of the 6 subject cohort described above, in which 3 to 5 sparse pharmacokinetic samples will be collected.

Efficacy will be based on a determination of global response (combination of clinical and microbiological response) of success or failure 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.

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

We plan to amend this protocol at a future time to allow for the enrollment of neonates (from 0 to 1 month of age) when additional pharmacokinetic data are available for this patient population.

Study Schematic:



5. Section 4. SUBJECT SELECTION, 4.1. Inclusion Criteria, beginning with number 1

Change From

3. 1. **Definitive** ~~D~~diagnosis of invasive candidiasis/candidemia (ICC) is based on the growth of *Candida* sp. from a blood and/or tissue culture obtained from a normally sterile site ~~within 96 hours before study entry.~~

For the purpose of study entry, a subject must have ~~Diagnosis will be based on presence of at least at least one microbiologic AND at least one clinical criteria listed below. of the following:~~

Microbiologic Criteria:

Subject must have at least one of the criteria listed below either at the time of study entry or within 96 hours prior to study entry.

- **Candidemia:** ~~a~~At least one blood culture positive for *Candida* sp. (in the absence of other demonstrated foci of infection) or;
- Other forms of invasive candidiasis:
 - ~~P~~positive culture for *Candida* sp. from a specimen from a normally sterile site (**other than blood**), with or without a positive blood culture;
 - ~~P~~positive culture for *Candida* sp. from a **percutaneous** drain (**eg, chest tube, intra-abdominal**) placed <24 hours in a normally sterile site;
 - ~~a~~~~P~~positive blood culture for *Candida* sp. plus ophthalmic examination consistent with Candida endophthalmitis;
 - Candida endocarditis: At least one positive blood culture for ~~Candida~~*Candida* sp. and evidence of endocarditis on echocardiogram;
 - Candida osteomyelitis: At least one positive culture for *Candida*~~Candida~~ sp. from a bone biopsy or aspirate and evidence of osteomyelitis on a magnetic resonance imaging (MRI) study;

Clinical Criteria:

Subject must have at least one of the criteria listed below either at the time of study entry or within 96 hours prior to study entry. ~~AND~~

~~At least one of the following:~~

- ~~A~~~~f~~**Fever**, defined as an oral/tympanic temperature $\geq 100.4^{\circ}\text{F}$ (38.0°C), rectal temperature $\geq 101.4^{\circ}\text{F}$ (38.6°C) or an axillary temperature $\geq 99.4^{\circ}\text{F}$ (37.4°C);

- **Hypothermia**, defined as a temperature less than 96.8°F (36.0°C);
- **Hypotension**, defined as ~~Aa~~ systolic blood pressure of less than 100% for age and gender norms (per National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents guidelines);⁷
- **Other Signs or symptoms of candidemia/invasive candidiasis**, which may include the following: feeding intolerance, bloody stools, abdominal distension, thrombocytopenia, lethargy, color change, hyperglycemia, glycosuria, unexplained metabolic acidosis.

**** Important Notes ****

Subjects may be enrolled in the study on the basis of mycologic 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 (eg, blood and/or tissue). However, in these subjects, culture confirmation of *Candida* sp. must be obtained within 96 hours post treatment initiation. If culture confirmation is not obtained within this time period, subjects will be discontinued from study treatment but will remain in the study for continued safety monitoring. These subject will be required to return for the 2-week and 6-week follow-up visits.

Positive cultures for *Candida* sp. from urine (in the absence of clinical signs and symptoms of pyelonephritis), sputum, bronchoalveolar lavage (BAL), endotracheal aspiration, gastric drainage or gastric aspiration do not qualify as a positive culture for study entry.

2. Male or female between the ages of 1 month and <18 years. Females of childbearing potential must have adequate contraception as determined by the Investigator for the duration of the trial.
3. For each subject, parent or legal guardian must be willing and able to provide signed and dated written informed consent documentation. Assent from the child or adolescent will be obtained as appropriate. This is to be obtained prior to enrollment.
4. Will be available for the duration of the study and be able to abide by the study restrictions.

Change To

1. Definitive diagnosis of invasive candidiasis/candidemia (ICC) is based on the growth of *Candida* sp. from a blood and/or tissue culture obtained from a normally sterile site.

For the purpose of study entry, a subject must have at least one microbiologic AND at least one clinical criteria listed below.

Microbiologic Criteria:

Subject must have at least one of the criteria listed below either at the time of study entry or within 96 hours prior to study entry.

- **Candidemia:** At least one blood culture positive for *Candida* sp. (in the absence of other demonstrated foci of infection) or;
- Other forms of invasive candidiasis:
 - Positive culture for *Candida* sp. from a specimen from a normally sterile site (other than blood), with or without a positive blood culture;
 - Positive culture for *Candida* sp. from a percutaneous drain (e.g., chest tube, intra-abdominal) placed <24 hours in a normally sterile site;
 - Positive blood culture for *Candida* sp. plus ophthalmic examination consistent with Candida endophthalmitis;
 - **Candida endocarditis:** At least one positive blood culture for *Candida* sp. and evidence of endocarditis on echocardiogram;
 - **Candida osteomyelitis:** At least one positive culture for *Candida* sp. from a bone biopsy or aspirate and evidence of osteomyelitis on a magnetic resonance imaging (MRI) study;

Clinical Criteria:

Subject must have at least one of the criteria listed below either at the time of study entry or within 96 hours prior to study entry.

- **Fever**, defined as an oral/tympanic temperature $\geq 100.4^{\circ}\text{F}$ (38.0°C), rectal temperature $\geq 101.4^{\circ}\text{F}$ (38.6°C) or an axillary temperature $\geq 99.4^{\circ}\text{F}$ (37.4°C);
- **Hypothermia**, defined as a temperature less than 96.8°F (36.0°C);
- **Hypotension**, defined as a systolic blood pressure of less than 100% for age and gender norms (per National High Blood Pressure Education Program (NHBPEP) Working Group on Children and Adolescents guidelines);⁷
- **Other signs or symptoms of candidemia/invasive candidiasis**, which may include the following: feeding intolerance, bloody stools, abdominal distension, thrombocytopenia, lethargy, color change, hyperglycemia, glycosuria, unexplained metabolic acidosis.

**** Important Notes ****

Subjects may be enrolled in the study on the basis of mycologic 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 (eg, blood and/or tissue). However, in these subjects, culture confirmation of *Candida* sp. must be obtained within 96 hours post treatment initiation. If culture confirmation is not obtained within this time period, subjects will be discontinued from study treatment but will remain in the study for continued safety monitoring. These subject will be required to return for the 2-week and 6-week follow-up visits.

Positive cultures for *Candida* sp. from urine (in the absence of clinical signs and symptoms of pyelonephritis), sputum, bronchoalveolar lavage (BAL), endotracheal aspiration, gastric drainage or gastric aspiration do not qualify as a positive culture for study entry.

2. Male or female between the ages of 1 month and <18 years. Females of childbearing potential must have adequate contraception as determined by the Investigator for the duration of the trial.
3. For each subject, parent or legal guardian must be willing and able to provide signed and dated written informed consent documentation. Assent from the child or adolescent will be obtained as appropriate. This is to be obtained prior to enrollment.
4. Will be available for the duration of the study and be able to abide by the study restrictions.

6. Section 4. SUBJECT SELECTION, 4.2. Exclusion Criteria, 2nd, paragraph, number 11, 3rd paragraph numbers 13- 15

Change From

**** Important Note **** Prior antifungal prophylaxis (ie, the use of an antifungal agent for the prevention of fungal infection) is allowed.

11. Subjects with suspected *Candida* osteomyelitis, endocarditis, or meningitis.

**** ImportantPlease Note **** If it is anticipated that a prosthetic device or vascular catheter cannot be removed within this time frame, the medical monitor should be contacted to discuss enrolment.

13. Subjects with a prosthetic heart valve or vascular graft suspected to be the site of the *Candida* infection and positive blood cultures.

14. Subjects with prosthetic or native valve *Candida* endocarditis who have not and/or cannot undergo valvular replacement surgery prior to or soon after study entry.

15. Subjects with *Candida* osteomyelitis associated with a prosthetic device in whom the prosthetic device has not been and/or cannot be removed surgically prior to or soon after study entry.

Change To

**** Important Note ** Prior antifungal prophylaxis (ie, the use of an antifungal agent for the prevention of fungal infection) is allowed.**

11. Subjects with suspected *Candida* meningitis.

**** Important Note ** If it is anticipated that a prosthetic device or vascular catheter cannot be removed within this time frame, the medical monitor should be contacted to discuss enrolment.**

13. Subjects with a vascular graft suspected to be the site of the *Candida* infection and positive blood cultures.

14. Subjects with prosthetic or native valve *Candida* endocarditis who have not and/or cannot undergo valvular replacement surgery prior to or soon after study entry.

15. Subjects with *Candida* osteomyelitis associated with a prosthetic device in whom the prosthetic device has not been and/or cannot be removed surgically prior to or soon after study entry.

7. Section 5. STUDY TREATEMENTS, 5.1. Allocation to Treatment, 4th and 5th bullets and 6-8th paragraphs

Change From

- **Eradication or presumed eradication** ~~Documentation of a negative culture for *Candida* spp. + *Candida* spp. from any other sites of infection if identified at enrollment;~~
- The specific *Candida* isolate identified at study entry is susceptible (or presumed to be susceptible based on the species identified and local *Candida* spp. resistance patterns) to fluconazole;

**** Important Note for Subjects with *Candida* Endocarditis and *Candida* Osteomyelitis****

The maximum total treatment duration in this study is 49 days, and the maximum allowed treatment duration with anidulafungin is 35 days. After at least 10 days of treatment with anidulafungin, subjects may be switched to oral fluconazole (provided switch criteria are met) to complete 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.

Change To

- Eradication or presumed eradication of *Candida* sp. from any other sites of infection if identified at enrollment;
- The specific *Candida* isolate identified at study entry is susceptible (or presumed to be susceptible based on the species identified and local *Candida* sp. resistance patterns) to fluconazole;

**** Important Note for Subjects with *Candida* Endocarditis and *Candida* Osteomyelitis****

The maximum total treatment duration in this study is 49 days, and the maximum allowed treatment duration with anidulafungin is 35 days. After at least 10 days of treatment with anidulafungin, subjects may be switched to oral fluconazole (provided switch criteria are met) to complete 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.

8. Section 5. STUDY TREATMENTS, 5.2.3. Administration, 2nd paragraph

Change From

Anidulafungin will be administered intravenously at an infusion rate not exceeding 1.1 mg/minute. Anidulafungin loading dose of 3.0 mg/kg (not to exceed 200 mg) on the first day of treatment should be administered intravenously **at a rate of 1.1 mg/min or less, however the actual duration of infusion time should not exceed the calculated duration of infusion time (based on 1.1 mg/min) plus an additional 30 minutes. For example, for a child weighing 25 kg, the calculated duration of infusion time (based on a rate of 1.1 mg/min) would be 68 minutes, and maximum duration of infusion would be 98 minutes (68 minutes plus 30 minutes).** ~~over no more than 180 minutes.~~

Anidulafungin maintenance dose of 1.5 mg/kg/day (not to exceed 100 mg) on subsequent days should be administered intravenously **at a rate of 1.1 mg/min or less, however the actual duration of infusion time should not exceed the calculated duration of infusion time (based on 1.1 mg/min) plus an additional 30 minutes.** For example, for a child weighing 25 kg, the calculated duration of infusion time (based on a rate of 1.1 mg/min) would be 34 minutes, and maximum duration of infusion would be 64 minutes (34 minutes plus 30 minutes). ~~over no more than 90 minutes.~~

**** Important Note **** In subjects who already initiated on IV anidulafungin prior to study entry, a repeat loading dose is not required. Instead, these subjects may be initiated on maintenance doses of IV anidulafungin.

Change To

Anidulafungin will be administered intravenously at an infusion rate not exceeding 1.1 mg/minute. Anidulafungin loading dose of 3.0 mg/kg (not to exceed 200 mg) on the first day of treatment should be administered intravenously at a rate of 1.1 mg/min or less, however the actual duration of infusion time should not exceed the calculated duration of infusion time (based on 1.1 mg/min) plus an additional 30 minutes. For example, for a child weighing 25 kg, the calculated duration of infusion time (based on a rate of 1.1 mg/min) would be 68 minutes, and maximum duration of infusion would be 98 minutes (68 minutes plus 30 minutes).

Anidulafungin maintenance dose of 1.5 mg/kg/day (not to exceed 100 mg) on subsequent days should be administered intravenously at a rate of 1.1 mg/min or less, however the actual duration of infusion time should not exceed the calculated duration of infusion time (based on 1.1 mg/min) plus an additional 30 minutes. For example, for a child weighing 25 kg, the calculated duration of infusion time (based on a rate of 1.1 mg/min) would be 34 minutes, and maximum duration of infusion would be 64 minutes (34 minutes plus 30 minutes).

**** Important Note **** In subjects who already initiated on IV anidulafungin prior to study entry, a repeat loading dose is not required. Instead, these subjects may be initiated on maintenance doses of IV anidulafungin.

9. Section 6. STUDY PROCEDURES, 6.1. Screening Visit, 1st paragraph, then from Note forward

Change From

The following screening activities **will be performed**~~should occur~~ following the informed consent and within two days prior to first dose.

- **** (Please Note **** Fundoscopic examination should be performed with pupil~~eyes~~ dilated if possible. In addition, when required by the protocol, the exam should be performed by an ophthalmologist unless it is not possible for practical reasons, in which case it may be performed by the principle investigator or subinvestigator. ~~If it is not possible to perform a fundoscopic examination prior to the first dose of study~~

drug, it may be performed within 48 hours of the first dose. Under extenuating circumstances, if a fundoscopic examination cannot be performed at baseline or within 48 hours, every effort should be made to perform the examination as soon as possible thereafter. ~~it may be performed up to 48 hours after the first dose);~~

- Record screening ~~B~~blood and/or tissue culture results (Note: If organism identity is pending, plan to record results on the case report form at a later time when the organism identity is determined and the results are available);s
- Obtain blood sample for blood culture if the day of the screening visit is also Day 1 of treatment. Otherwise, a blood sample for blood culture is not required until the first day of treatment (Day 1), just prior to the administration of study drug;
- (to be obtained within 96 hours before first dose of Study Drug: Day 1);
- Specimen culture (from other normally sterile sites as clinically indicated);
- CBC with differential (Complete blood count with differential and RBC count with reticulocyte count and platelets count);
- Serum chemistry [Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline-Phosphatase (Alk-Phos), Total Bilirubin, Albumin, Bicarbonate, Glucose, Urea nitrogen (BUN), Creatinine (Cr), Sodium (Na), Potassium (K), Calcium (Ca), Chloride (Cl), and Magnesium (Mg)].
- For subjects with Candida endocarditis: Perform echocardiogram, either transesophageal (preferred) or transthoracic;
- ** Please Note ** If an echocardiogram was already performed within the previous 96 hours (of the screening visit), then a echocardiogram at the time of screening is not required. In this case, the results of the echocardiogram used to support the diagnosis of Candida endocarditis will be reported in the case report form.
- For subjects with Candida osteomyelitis: Perform magnetic resonance imaging (MRI) study of affected area;
- ** Please Note ** If an MRI was already performed within the previous 96 hours (of the screening visit), then an MRI at the time of screening is not required. In this case, the results of the MRI used to support the diagnosis of Candida osteomyelitis will be reported in the case report form.

Change To

The following screening activities will be performed following the informed consent and within two days prior to first dose.

- **** Please Note **** Fundoscopic examination should be performed with pupils dilated if possible. In addition, when required by the protocol, the exam should be performed by an ophthalmologist unless it is not possible for practical reasons, in which case it may be performed by the principle investigator or subinvestigator. If it is not possible to perform a fundoscopic examination prior to the first dose of study drug, it may be performed within 48 hours of the first dose. Under extenuating circumstances, if a fundoscopic examination cannot be performed at baseline or within 48 hours, every effort should be made to perform the examination as soon as possible thereafter.
- Record screening blood and/or tissue culture results (Note: If organism identity is pending, plan to record results on the case report form at a later time when the organism identity is determined and the results are available);
- Obtain blood sample for blood culture if the day of the screening visit is also Day 1 of treatment. Otherwise, a blood sample for blood culture is not required until the first day of treatment (Day 1), just prior to the administration of study drug;
- CBC with differential (Complete blood count with differential and RBC count with reticulocyte count and platelets count);
- Serum chemistry [Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline-Phosphatase (Alk-Phos), Total Bilirubin, Albumin, Bicarbonate, Glucose, Urea nitrogen (BUN), Creatinine (Cr), Sodium (Na), Potassium (K), Calcium (Ca), Chloride (Cl), and Magnesium (Mg)].
- **For subjects with Candida endocarditis:** Perform echocardiogram, either transesophageal (preferred) or transthoracic;
- **** Please Note **** If an echocardiogram was already performed within the previous 96 hours (of the screening visit), then a echocardiogram at the time of screening is not required. In this case, the results of the echocardiogram used to support the diagnosis of Candida endocarditis will be reported in the case report form.
- **For subjects with Candida osteomyelitis:** Perform magnetic resonance imaging (MRI) study of affected area;
- **** Please Note **** If an MRI was already performed within the previous 96 hours (of the screening visit), then an MRI at the time of screening is not required. In this case, the results of the MRI used to support the diagnosis of Candida osteomyelitis will be reported in the case report form.

10. Section 6. STUDY PROCEDURES, 6.2.1. Daily, Through End of Treatment, 2nd bullet

Change From

- Record ~~T~~temperature (Note: Subjects receiving treatment in the outpatient setting may have less frequent assessments), but not less than at least once every 7 days. Close monitoring of subjects treated in the outpatient setting is required);

Change To

- Record temperature (Note: Subjects receiving treatment in the outpatient setting may have less frequent assessments, but not less than at least once every 7 days. Close monitoring of subjects treated in the outpatient setting is required);

11. Section 6. STUDY PROCEDURES, 6.2.2. Days 1 and 2 ONLY for Sub-study Subjects (first 6 subjects aged 1 month to <2 years at selected sites), 2nd paragraph, 2nd bullet and , 5th and 6th paragraphs

Change From

Pharmacokinetic sampling: Six (6) blood samples (0.3-0.5 ml each to provide 0.1 – 0.2 mL plasma) will be collected for anidulafungin measurement at the following time points:

- **On Day 2:** jJust prior to the start of infusion; 2 minutes before the end of infusion, 6 hours after start of infusion, 12 hours after start of infusion, and 24 hours after start of infusion.

**** Important Note **** For subjects in whom the investigator has chosen to administer anidulafungin in combination with a second antifungal agent, these subjects will be discontinued from treatment following completion of pharmacokinetic sampling but will remain in the study for continued safety assessments and are required to return for the 2-week and 6-week follow-up visits.

For subjects in whom the investigator has chosen to administer anidulafungin as monotherapy, following completion of pharmacokinetic sampling these subjects will continued to be treated with anidulafungin 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.

Change To

Pharmacokinetic sampling: Six (6) blood samples (0.3-0.5 ml each to provide 0.1 – 0.2 mL plasma) will be collected for anidulafungin measurement at the following time points:

- **On Day 2:** Just prior to the start of infusion; 2 minutes before the end of infusion, 6 hours after start of infusion, 12 hours after start of infusion, and 24 hours after start of infusion.

**** Important Note **** For subjects in whom the investigator has chosen to administer anidulafungin in combination with a second antifungal agent, these subjects will be discontinued from treatment following completion of pharmacokinetic sampling but will remain in the study for continued safety assessments and are required to return for the 2-week and 6-week follow-up visits.

For subjects in whom the investigator has chosen to administer anidulafungin as monotherapy, following completion of pharmacokinetic sampling these subjects will continued to be treated with anidulafungin 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.

12. Section 6. STUDY PROCEDURES, 6.2.4. Day 3, 2nd bullet

Change From

- Blood cultures (unless two consecutive blood cultures, separated by at least 24 hours, has been confirmed to be negative);

Change To

- Blood cultures (unless two consecutive blood cultures, separated by at least 24 hours, has been confirmed to be negative);

13. Section 6. STUDY PROCEDURES, 6.2.5. Day 7, 2nd bullet

Change From

- Blood cultures (unless two consecutive blood cultures, separated by at least 24 hours, has been confirmed to be negative);

Change To

- Blood cultures (unless two consecutive blood cultures, separated by at least 24 hours, has been confirmed to be negative);

14. Section 6. STUDY PROCEDURES, 6.2.7. Days 11 to 34 (Day Prior to Last Day of IV Anidulafungin Therapy – Maximum is 35 Days on Anidulafungin), 1st bullet

Change From

- Perform ~~T~~targeted physical examination (including vital signs) every 3 days (Note: Subjects receiving treatment in the outpatient setting may have less frequent assessments, but not less than at least once every 7 days. Close monitoring of subjects treated in the outpatient setting is required);

Change To

- Perform targeted physical examination (including vital signs) every 3 days (Note: Subjects receiving treatment in the outpatient setting may have less frequent assessments, but not less than at least once every 7 days. Close monitoring of subjects treated in the outpatient setting is required);

15. Section 6. STUDY PROCEDURES, 6.3. End of Anidulafungin Therapy, 1st paragraph and 8th bullet, 2nd paragraph, 9th bullet, and 3rd paragraph

Addition

The following assessment will be performed on the last day (or within 24 hours of the last day) of IV anidulafungin treatment:

- Echocardiogram, either transesophageal (preferred) or transthoracic (to be performed only in subjects with Candida endocarditis)
- ** Please Note ** To be performed at the End of Treatment with IV anidulafungin in subjects who are not switched to oral fluconazole. In subjects who are switched to oral fluconazole, echocardiogram should be deferred to the End of Oral Therapy visit.
- Magnetic Resonance Imaging (MRI) study (to be performed only in subjects with Candida osteomyelitis);
- ** Please Note ** To be performed at the End of Treatment with IV anidulafungin in subjects who are not switched to oral fluconazole. In subjects who are switched to oral fluconazole, echocardiogram should be deferred to the End of Oral Therapy visit.

16. Section 6. STUDY PROCEDURES, 6.4. End of Oral Therapy (if applicable), 1st paragraph, 8th and 9th bullets and 2nd paragraph

Change From

The following assessment will be performed on the last day (or within 24 hours of the last day) of IV anidulafungin treatment:

- Echocardiogram, either transesophageal (preferred) or transthoracic (to be performed only in subjects with Candida endocarditis);
- Magnetic Resonance Imaging (MRI) study (to be performed only in subjects with Candida osteomyelitis);

**** Please Note **** The EOT is defined as either (1) the end of IV anidulafungin if subject is not switched to oral fluconazole, or (2) the end of the oral fluconazole if subject is switched from IV anidulafungin to oral fluconazole.

Change To

The following assessment will be performed on the last day (or within 24 hours of the last day) of IV anidulafungin treatment:

- Echocardiogram, either transesophageal (preferred) or transthoracic (to be performed only in subjects with Candida endocarditis);
- Magnetic Resonance Imaging (MRI) study (to be performed only in subjects with Candida osteomyelitis);

**** Please Note **** The EOT is defined as either (1) the end of IV anidulafungin if subject is not switched to oral fluconazole, or (2) the end of the oral fluconazole if subject is switched from IV anidulafungin to oral fluconazole.

17. Section 6. STUDY PROCEDURES, 6.5. Follow Up Visit (End of Treatment +2 weeks), 1st paragraph and 5th and 6th bullets

Change From

The following assessment will be performed 2-weeks (or within 2 days of the scheduled 2-week follow-up visit) after the last dose of study drug treatment:

- Blood cultures (only if clinically indicated);
- Specimen culture (from other normally sterile sites, **only if** ~~as~~ clinically indicated);

Change To

The following assessment will be performed 2-weeks (or within 2 days of the scheduled 2-week follow-up visit) after the last dose of study drug treatment:

- Blood cultures (only if clinically indicated);
- Specimen culture (from other normally sterile sites, only if clinically indicated);

18. Section 6. STUDY PROCEDURES, 6.6. Long Term Follow-Up (End of Treatment + 6 weeks), 1st paragraph and 5th bullet

Change From

The following assessment will be performed 6-weeks (or within 1 week of the scheduled 6-week follow-up visit) after the last dose of study drug treatment:

- Blood cultures (only if clinically indicated);

Change To

The following assessment will be performed 6-weeks (or within 1 week of the scheduled 6-week follow-up visit) after the last dose of study drug treatment:

- Blood cultures (only if clinically indicated);

19. Section 6. STUDY PROCEDURES, 6.9. Discontinuation Criteria for Abnormal Liver Function Tests, last paragraph

Change From

Note: These subjects will be discontinued from study treatment but will remain in the study for safety monitoring according to the procedures described in section 6.7. **These subjects are required to return for the 2- and 6-week follow-up visits.**

Change To

Note: These subjects will be discontinued from study treatment but will remain in the study for safety monitoring according to the procedures described in section 6.7. These subjects are required to return for the 2- and 6-week follow-up visits.

20. Section 6. STUDY PROCEDURES, 6.10. Discontinuation Criteria for Persistent Candidemia, last paragraph

Change From

Note: These subjects will be discontinued from study treatment but will remain in the study for safety monitoring according to the procedures described in section 6.7. **These subjects are required to return for the 2- and 6-week follow-up visits.**

Change To

Note: These subjects will be discontinued from study treatment but will remain in the study for safety monitoring according to the procedures described in section 6.7. These subjects are required to return for the 2- and 6-week follow-up visits.

21. Section 7. ASSESSMENTS, 7.1. Clinical Assessments, letter d

Addition

- e. d. Signs and symptoms of Candida infection: The signs and symptoms of Candida infection are diverse and dependent on disease severity, the site of infection and status of the host immune system. Constitutional symptoms suggestive of systemic infection include fever and sepsis (eg, tachycardia, hypotension). Infection of visceral organ(s) typically manifest as organ dysfunction and may include radiologic findings demonstrative of singular or multiple microabscesses. The most frequently observed signs and symptoms of commonly encountered forms of candidiasis are listed in the Case Report Form. However, the investigator is referred to the most recent clinical practice guidelines (published in March 2009), from the Infectious Diseases Society of America on the management of Candidiasis for comprehensive review of signs and symptoms associated with this disease.⁸

22. Section 7. ASSESSMENTS, 7.2. Global Response Determination, bullets

Change From

- **Success**: ~~a~~A subject will be categorized as a success if there is both a clinical success (**cure or improvement**) and microbiological success (**eradication or presumed eradication**);
- **Failure**: ~~a~~A subject will be categorized as a failure if there is either a clinical or microbiological failure (excluding clinical and microbiological responses of indeterminate);
- **Indeterminate**: ~~a~~A subject will be categorized as indeterminate if there is a clinical and/or microbiological response of indeterminate and neither response was a failure.

Change To

- **Success**: A subject will be categorized as a success if there is both a clinical success (cure or improvement) and microbiological success (eradication or presumed eradication);
- **Failure**: A subject will be categorized as a failure if there is either a clinical or microbiological failure (excluding clinical and microbiological responses of indeterminate);
- **Indeterminate**: A subject will be categorized as indeterminate if there is a clinical and/or microbiological response of indeterminate and neither response was a failure.

**23. Section 7. ASSESSMENTS, 7.3, Clinical and Microbiologic Response Assessment,
7.3.1. Subjects with Invasive Candidiasis/Candidemia (Except for Subjects with
Candida Endocarditis or Candida Osteomyelitis), titles**

Additions

7.3. Clinical and Microbiologic Response Assessment,

**7.3.1. Subjects with Invasive Candidiasis/Candidemia (Except for Subjects with
Candida Endocarditis or Candida Osteomyelitis),**

**24. Section 7. ASSESSMENTS, 7.3.1.1. Clinical Response at End of IV Treatment
(EOIVT) and End of Treatment (EOT), title and section**

Change From

**7.3.1.1. Clinical Response at End of IV Treatment (EOIVT) and End of Treatment
(EOT)**

The components of global response will be defined as follows:

Clinical ~~r~~Response is defined as follows:

Success:

Success:

- **Cure:** Resolution of signs and symptoms attributed to *Candida* infection; no additional systemic antifungal; ~~treatment, or oral fluconazole required to complete the course of therapy;~~
- **Improvement:** Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal ~~treatment, or additional oral fluconazole required;~~
- Failure:
- **Failure: 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:
- **Indeterminate:** ~~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 a clinical efficacy response of indeterminate.

Change To

7.3.1.1. Clinical Response at End of IV Treatment (EOIVT) and End of Treatment (EOT)

Clinical response is defined as follows:

- **Cure:** Resolution of signs and symptoms attributed to *Candida* infection; no additional systemic antifungal;
- **Improvement:** Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal;
- **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 a clinical efficacy response of indeterminate.

25. Section 7. ASSESSMENTS, 7.3.1.2. Microcrobilogic Response at End of IV Treatment (EOIVT) and End of Treatment (EOT), title and section

Change From

7.3.1.2. Microcrobilogic Response ~~Microbiological Response~~ at End of IV Treatment (EOIVT) and End of Treatment (EOT)

Microbiologic response is defined as follows:

- Success:
- Success:
- **Eradication or presumed eradication:** Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful outcome.
- Failure:
- Failure:
- **Persistence (documented or presumed):** Any baseline *Candida* spp. is present in repeat cultures, or culture data are not available for subject with a clinical outcome of failure.
- Indeterminate:

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

Change To

7.3.1.2. Microbiologic Response at End of IV Treatment (EOIVT) and End of Treatment (EOT)

Microbiologic response is defined as follows:

- **Eradication or presumed eradication**: Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful outcome.
- **Persistence (documented or presumed)**: Any baseline *Candida* spp. 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.

26. Section 7. ASSESSMENTS, 7.3.1.3. Clinical Response at the 2-Week and 6- Week Follow-Up Visits, title and section

Change From

~~7.3.1.3. At the 2 Week and 6 Week Follow Up Visit~~

~~7.3.1.4. Subjects with Invasive Candidiasis/Candidemia (Excluding Subjects with Candida Endocarditis and Osteomyelitis)~~

7.2.1.3. Clinical Response at the 2-Week and 6-Week Follow-Up Visits

Clinical response is defined as follows:

~~Clinical Response~~

~~———Success:~~

Cure: Resolution of signs and symptoms attributed to *Candida* infection; no additional systemic antifungal

- **Improvement**: Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal.
- **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 a clinical efficacy response of indeterminate.

Change To

7.3.1.3. Clinical Response at the 2-Week and 6- Week Follow-Up Visits,

Clinical response is defined as follows:

Cure: Resolution of signs and symptoms attributed to *Candida* infection; no additional systemic antifungal

- **Improvement:** Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal.
- **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 a clinical efficacy response of indeterminate.

27. Section 7. ASSESSMENTS, 7.3.1.4. Microbiologic Response at the the 2- Week and 6- Week Follow-Up Visits, Title and section

Change From

7.3.1.4. Microbiologic Response at the 2-Week and 6-Week Follow-Up Visits

Microbiologic response is defined as follows:

- ~~**Success:**~~
- **Eradication or presumed eradication:** Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful outcome.
- ~~**Failure:**~~
- **Persistence (documented or presumed):** Any baseline *Candida* spp. 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.

- The following definitions will be used for assessments made at the FU visits:
- The following definitions will be used for assessments made at the FU visits:
- **Relapse (recurrence):** Any baseline *Candida* spp 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;
- **New Infection:** Subject presenting with clinical failure with the emergence of new *Candida* spp at the original site of infection or at a distant site of infection;

Change To

7.3.1.4. Microbiologic Response at the 2-Week and 6-Week Follow-Up Visits

Microbiologic response is defined as follows:

- **Eradication or presumed eradication:** Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful outcome.
- **Persistence (documented or presumed):** Any baseline *Candida* spp. 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* spp 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;
- **New Infection:** Subject presenting with clinical failure with the emergence of new *Candida* spp at the original site of infection or at a distant site of infection;

28. Section 7. ASSESSMENTS, 7.3.2. Continued Complete Resoution/Improvment

Deletion

~~7.3.2. Continued Complete Resolution/Improvement:~~

~~Subjects who are evaluated as completely resolved of infection or improved at the end of treatment evaluation and whose condition remains stable at the follow-up evaluation.~~

29. Section 7. ASSESSMENTS, 7.3.2. Subjects with Candida Endocarditis and Candida Osteomyelitis Only, title

Addition and sections renumbered accordingly

7.3.2. Subjects with Candida Endocarditis and Candida Osteomyelitis Only

30. Section 7. ASSESSMENTS, 7.3.2.1., Clinical Response at End of IV Treatment (EOIVT) and End of Treatment (EOT), and 7.3.2.2. Microbiologic Response at End of IV Treatment (EOIVT) and End of Treatment (EOT), and 7.3.2.3. Clinical Response at the 2-Week and 6-Week Follow-Up Visits

Additions and sections renumbered accordingly

7.3.2.1. Clinical Response at End of IV Treatment (EOIVT) and End of Treatment (EOT)

Clinical response is defined as follows:

- **Cure:** Resolution of signs and symptoms attributed to *Candida* infection; no additional/ongoing systemic antifungal therapy;
- **Improvement:** Significant, but incomplete resolution of signs and symptoms of the *Candida* infection;
- **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 a clinical efficacy response of indeterminate.

7.3.2.2. Microbiologic Response at End of IV Treatment (EOIVT) and End of Treatment (EOT)

Microbiologic response is defined as follows:

- **Eradication or presumed eradication:** Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful outcome.
- **Persistence (documented or presumed):** Any baseline *Candida* spp. 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.

7.3.2.3. Clinical Response at the 2-Week and 6-Week Follow-Up Visits

Clinical response is defined as follows:

- **Cure:** Resolution of signs and symptoms attributed to *Candida* infection; no additional/ongoing systemic antifungal;
- **Improvement:** Significant, but incomplete resolution of signs and symptoms of the *Candida* infection;
- **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 a clinical efficacy response of indeterminate.

31. Section 7. ASSESSMENTS, 7.3.2.4. Micro Response at the 2-Week and 6-Week Follow-Up Visits, title and section

Change From

7.3.2.4. Micro Response at the 2-Week and 6-Week Follow-Up Visits

Microbiologic response is defined as follows:

- **Eradication or presumed eradication:** Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful outcome;
- **Persistence (documented or presumed):** Any baseline *Candida* spp. 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* spp 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;
- **New Infection:** Subject presenting with clinical failure with the emergence of new *Candida* spp at the original site of infection or at a distant site of infection.

In addition, subjects will be contacted (eg, in person, by telephone, mail, or e-mail) to determine survival status at 2-Week and 6-Week after EOT. If a subject cannot be contacted, survival status may be obtained through a family member, hospital/clinic records or information that is in the public domain.

Change To

7.3.2.4. Micro Response at the 2-Week and 6-Week Follow-Up Visits

Microbiologic response is defined as follows:

- **Eradication or presumed eradication:** Baseline pathogen not isolated from original site culture(s), or culture data are not available for a subject with successful outcome;
- **Persistence (documented or presumed):** Any baseline *Candida* spp. 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* spp 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;
- **New Infection:** Subject presenting with clinical failure with the emergence of new *Candida* spp at the original site of infection or at a distant site of infection.

In addition, subjects will be contacted (eg, in person, by telephone, mail, or e-mail) to determine survival status at 2-Week and 6-Week after EOT. If a subject cannot be contacted, survival status may be obtained through a family member, hospital/clinic records or information that is in the public domain.

32. Section 7. ASSESSMENTS, 7.4. Fundoscopic Examinations

Change From

Fundoscopy exams should be performed with pupils dilated if possible. In addition, when required by the protocol, the exam should be performed by an ophthalmologist unless it is not possible for practical reasons, in which case it may be performed by **the Principle investigator or subinvestigator(s)** ~~a non-ophthalmologist~~.

If it is not possible to perform a fundoscopic examination prior to the first dose of study drug, it may be performed up to 48 hours after the first dose. Under extenuating circumstances, if a fundoscopic examination cannot be performed prior to the first dose or within 48 hours, every effort should be made to perform the examination as soon as possible thereafter.

**** Please Note ** If the baseline fundoscopic examination is positive for findings consistent with Candida endophthalmitis, then a repeat fundoscopic examination is required at the end of treatment and at the 2- and 6-week follow-up visits. Additional fundoscopic assessments, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional fundoscopic examinations are performed, the results should be recorded on the case report form.**

Change To

Fundoscopic exams should be performed with pupils dilated if possible. In addition, when required by the protocol, the exam should be performed by an ophthalmologist unless it is not possible for practical reasons, in which case it may be performed by the Principle investigator or subinvestigator(s).

If it is not possible to perform a fundoscopic examination prior to the first dose of study drug, it may be performed up to 48 hours after the first dose. Under extenuating circumstances, if a fundoscopic examination cannot be performed prior to the first dose or within 48 hours, every effort should be made to perform the examination as soon as possible thereafter.

**** Please Note **** If the baseline fundoscopic examination is positive for findings consistent with Candida endophthalmitis, then a repeat fundoscopic examination is required at the end of treatment and at the 2- and 6-week follow-up visits. Additional fundoscopic assessments, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional fundoscopic examinations are performed, the results should be recorded on the case report form.

33. Section 7. ASSESSMENTS, 7.6.1. Hematology and Blood Chemistry

Change From

The study sites will process routine hematology and blood chemistry specimens locally.

- CBC with differential (Hematology panel) will include: red blood cell count, reticulocytes (absolute or percent), white blood cell count, neutrophils (absolute or percent), lymphocytes (absolute or percent), monocytes (absolute or percent), basophils (absolute or percent) and platelets;
- Serum Chemistry will include: sodium, potassium, chloride, bicarbonate, BUN (or urea), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, albumin, glucose, calcium, magnesium.

Change To

The study sites will process routine hematology and blood chemistry specimens locally.

- CBC with differential (Hematology panel) will include: red blood cell count, reticulocytes (absolute or percent), white blood cell count, neutrophils (absolute or percent), lymphocytes (absolute or percent), monocytes (absolute or percent), basophils (absolute or percent) and platelets;
- Serum Chemistry will include: sodium, potassium, chloride, bicarbonate, BUN (or urea), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, albumin, glucose, calcium, magnesium.

34. Section 7. ASSESSMENTS, 7.6.2. Echocardiogram (For Subjects with Candida Endocarditis and 7.6.3. Magnetic Resonance Imaging (MRI) Studies (For Subjects with Candida Osteomyelitis)

Additions and sections renumbered accordingly

7.6.2. Echocardiogram (For Subjects with Candida Endocarditis)

For subjects with Candida endocarditis, either a transesophageal (preferred) or transthoracic echocardiogram will be performed at the time of screening. If, however, the test was already performed within the previous 96 hours (of the screening visit), then an echocardiogram at the time of screening is not required. In this case, results of the echocardiogram used to support the initial diagnosis will be recorded in the case report form.

An echocardiogram will also be performed at the end of study treatment (ie, at the end of treatment with IV anidulafungin, or at the end of treatment with oral fluconazole in subjects who are switched to oral therapy). Results of the echocardiogram will be recorded on the appropriate case report form.

Additional echocardiogram assessments, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional echocardiogram assessments are performed, the results should be recorded on the case report form.

**** Important Note **** In subjects with Candida endocarditis 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.

7.6.3. Magnetic Resonance Imaging (MRI) Studies (For Subjects with Candida Osteomyelitis)

For subjects with *Candida* osteomyelitis, a magnetic resonance imaging (MRI) study will be performed at the time of screening. If, however, the test was already performed within the previous 96 hours (of the screening visit), then an MRI at the time of screening is not required. In this case, results of the MRI used to support the initial diagnosis will be recorded in the case report form.

A magnetic resonance imaging (MRI) study of the affected area will also be performed at the end of study treatment (ie, at the end of treatment with IV anidulafungin, or at the end of treatment with oral fluconazole in subjects who are switched to oral therapy). Results of the MRI study will be recorded on the appropriate case report form.

Additional MRI studies, other than those required by the protocol, should also be performed as clinically indicated and according to local practice standards. In the event additional MRI studies are performed, the results should be recorded on the case report form.

**** Important Note ** In subjects with *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.**

35. Section 7. ASSESSMENTS, 7.6.4. Mycologic Testing for *Candida* Infection, Title

Change From

7.6.4. Mycologic Diagnostic Testing for *Candida* Infection

Change To

7.6.4. Mycologic Testing for *Candida* Infection

36. Section 7. ASSESSMENTS, 7.6.5. Microbiological Determinations

Change From

1. Screening Blood Culture(s): TheA 'screening visit blood culture' is the culture result that qualifies the subject for study entry (along with other inclusion criteria) and is from a blood or tissue sample (obtained from a normally sterile) that was obtained ~~will be obtained~~ within 96 hours prior to the screening visit, ~~before the first dose of Study Drug (Day 1)~~ that is positive for *Candida*~~Candida~~ sp.. The result of this culture will be recorded on the 'screening visit' case report form.

2. In the event the subject is enrolled on the basis of mycologic evidence suggestive of *Candida* infection (see Section 4.1, Inclusion Criteria) and the organism has not yet been identified, once the final identification has been determined the result will be recorded on the 'screening visit' case report form.

3. For the screening blood culture, it is preferable for two (2) aerobic blood cultures to be obtained from two (2) separate sites, however, if this is not practical for clinical reasons, the required screening blood cultures may be collected according to local practice standards and as the clinical circumstances dictate. If the screening positive baseline culture was drawn >96 hours before the start of treatment, the blood cultures should be repeated. If the screening blood samples for culture were taken <96 hours before study entry, blood cultures do not need to be repeated. Peripheral venipuncture is the preferred method for obtaining blood cultures.

Screening cultures for specimens other than blood: Obtained as clinically indicated.

4. On-Study Cultures:

a. Blood cultures: Blood cultures will be obtained **on Day 1 (prior to the administration of the first dose) in all subjects, at screening and then** every three (3) days thereafter (ie, on Day 3, ~~and 7, etc.~~) until two (2) consecutive cultures, separated by at least 24 hours, are confirmed to be negative while on study medication.

b. Blood cultures will also be obtained at the end of IV therapy (EOIVT), and at the end of oral therapy (in subjects switched to oral fluconazole). A blood culture at the 2-week and 6-week follow-up visit is required only if clinically indicated. ~~and at the early and late follow-up visits.~~

c. Additional cultures beyond those required by the protocol may be obtained at any time at the investigator's discretion, as clinically indicated. The results of the cultures should be recorded on the case report form.

4. **Tissue Cultures:** ~~Other than Blood:~~ For subjects whose **screening cultures** ~~baseline isolates (or histological evidence of infection)~~ were obtained from **sterile site** samples (other than blood), **follow-up cultures** ~~culture or histology~~ from the same **anatomical** site should be repeated **only** as clinically indicated, **otherwise they are not required.**

Investigators will send specimens (blood or other) to their local certified laboratory for culture (incubation should be a minimum of five days if not positive before then). Each laboratory will follow its usual procedures for identification of the species and susceptibility testing to marketed agents.

Additionally, all *Candida* isolates must be preserved for shipment to the reference laboratory for further identification, including speciation, and susceptibility testing. This includes the original isolate that the diagnosis for inclusion into the study was made, **as well as all**

subsequently recovered *Candida* isolates from any site. If more than one species of *Candida* is isolated from a single culture, all isolates must be sent to the reference laboratory. The susceptibility testing will be conducted using the current Clinical and Laboratory Standards Institute (CLSI) approved standard method.

Change To

1. Screening Culture(s): The ‘screening visit culture’ is the culture result that qualifies the subject for study entry (along with other inclusion criteria) and is from a blood or tissue sample (obtained from a normally sterile) that was obtained within 96 hours prior to the screening visit, that is positive for *Candida* sp.. The result of this culture will be recorded on the ‘screening visit’ case report form.

2. In the event the subject is enrolled on the basis of mycologic evidence suggestive of *Candida* infection (see Section 4.1, Inclusion Criteria) and the organism has not yet been identified, once the final identification has been determined the result will be recorded on the ‘screening visit’ case report form.

3. On-Study Cultures:

a. Blood cultures: Blood cultures will be obtained on Day 1 (prior to the administration of the first dose) in all subjects, and then every three (3) days thereafter (ie, on Day 3, 7, etc.) until two (2) consecutive cultures, separated by at least 24 hours, are confirmed to be negative while on study medication.

b. Blood cultures will also be obtained at the end of IV therapy (EOIVT), and at the end of oral therapy (in subjects switched to oral fluconazole). A blood culture at the 2-week and 6-week follow-up visit is required only if clinically indicated.

c. Additional cultures beyond those required by the protocol may be obtained at any time at the investigator’s discretion, as clinically indicated. The results of the cultures should be recorded on the case report form.

4. Tissue Cultures: For subjects whose screening cultures were obtained from sterile site samples (other than blood), follow-up cultures from the same anatomical site should be repeated only as clinically indicated, otherwise they are not required.

Investigators will send specimens (blood or other) to their local certified laboratory for culture (incubation should be a minimum of five days if not positive before then). Each laboratory will follow its usual procedures for identification of the species and susceptibility testing to marketed agents.

Additionally, all *Candida* isolates must be preserved for shipment to the reference laboratory for further identification, including speciation, and susceptibility testing. This includes the original isolate that the diagnosis for inclusion into the study was made, as well as all subsequently recovered *Candida* isolates from any site. If more than one species of *Candida* is isolated from a single culture, all isolates must be sent to the reference laboratory. The

susceptibility testing will be conducted using the current Clinical and Laboratory Standards Institute (CLSI) approved standard method.

37. Section 7. ASSESSMENTS, 7.7.1. Blood Sampling for Subjects in the PK Sub-Study (1 Month to <2 Years of Age), 2nd bullet

Change From

- **On Day 2 (receiving 1.5 mg/kg IV infusion):** Just prior to the start of infusion; 2 minutes before the end of infusion, 6, 12 and 24 hours after the start of infusion.

Change To

- **On Day 2 (receiving 1.5 mg/kg IV infusion):** Just prior to the start of infusion; 2 minutes before the end of infusion, 6, 12 and 24 hours after the start of infusion.

38. Section 9. DATA ANALYSIS/STATISTICAL METHODS, 9.2. Analysis of Secondary Endpoints, 2nd paragraph

Deletion

~~Supportive analyses of the main efficacy endpoint will be performed in the Intent to Treat (ITT) population, consisting of all randomized subjects.~~

39. Section 16. REFERENCES, numbers 5 and 8

Change From

5. Anidulafungin Investigator Brochure. **June May-201009.**
8. Pappas PG, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD. Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 20009. 48:503-535.

Change To

5. Anidulafungin Investigator Brochure. June 2010.
8. Pappas PG, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE, Filler SG, Fisher JF, Kullberg BJ, Ostrosky-Zeichner L, Reboli AC, Rex JH, Walsh TJ, Sobel JD. Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 20009. 48:503-535.

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