NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA - Efficacy Supplement (S-027) sNDA - Prior Approval Labeling Supplement (S-029)
Application Number(s)	021632, S-027; SDN 341 021632, S-029; SDN 345
Priority or Standard	Standard
Submit Date(s)	11.22.2019 (S-027) 03.25.2020 (S-029)
Received Date(s)	11.22.2019 (S-027) 03.25.2020 (S-029)
PDUFA Goal Date	09.22.2020 (S-027) 09.25.2020 (S-029)
Division/Office	Division of Anti-Infectives/Office of Infectious Diseases
Review Completion Date	09.21.2020
Established/Proper Name	Anidulafungin
Trade Name	ERAXIS®
Pharmacologic Class	Echinocandin
Applicant	Vicuron Holdings LLC, a subsidiary of Pfizer Inc.
Dosage form	Lyophilized powder for injection, 50 mg or 100 mg per vial
Applicant proposed Dosing Regimen	3 mg/kg (not to exceed 200 mg) loading dose on Day 1, followed by 1.5 mg/kg (not to exceed 100 mg) daily dose thereafter for at least 14 days after the last positive culture
Applicant Proposed Indication(s)/Population(s)	Treatment of Candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in pediatric patients, 1 month of age and older.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Candidemia (disorder); Candidiasis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Dosing Regimen	3 mg/kg (not to exceed 200 mg) loading dose on Day 1, followed by 1.5 mg/kg (not to exceed 100 mg) daily dose thereafter for at least 14 days after the last positive culture
Link to submissions	sNDA: \\CDSESUB1\evsprod\NDA021632\0091 Prior Approval Labeling Supplement: \\CDSESUB1\evsprod\NDA021632\0096

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OPQ=Office of Pharmaceutical Quality
PeRC Team=Pediatric Review Committee
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSIS= Office of Study Integrity and Surveillance
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
EC	esophageal candidiasis
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HFI	hereditary fructose intolerance
ICC	candidemia and other invasive *Candida* infections
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Anidulafungin (ERAXIS®) is an echinocandin antifungal drug which exhibits fungicidal activity against *Candida* species. It is an inhibitor of 1, 3-β-D-glucan synthase, an enzyme that is not present in mammalian cells but is required by many pathogenic fungi for the synthesis of β-linked glucan, a component of the fungal cell wall.

Anidulafungin was approved in the United States on February 17, 2006 for the treatment of candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) and esophageal candidiasis in adults. As of December 31, 2018, intravenous (IV) anidulafungin has been approved in 96 countries and is currently marketed in 81 countries. Anidulafungin is administered as an initial loading dose of 200 mg IV on day 1 followed by 100 mg IV daily for treatment of candidemia and other forms of invasive candidiasis including intra-abdominal abscess and peritonitis. Anidulafungin is dosed as an initial loading dose of 100 mg IV and 50 mg IV daily for treatment of esophageal candidiasis. Anidulafungin is not recommended for *Candida* infections of the urinary tract, eye, and central nervous system in current treatment guidelines.[1]

In this supplemental NDA (S-027), the Applicant seeks to update the ERAXIS USPI with a new indication in pediatric patients 1 month to 17 years of age with candidemia and other invasive *Candida* infections based on the results of study A8851008. Study A8851008 is a prospective, open-label study to assess the pharmacokinetics, safety & efficacy of anidulafungin when used to treat children with invasive candidiasis, including candidemia. The proposed pediatric dose is 3 mg/kg IV (not to exceed 200 mg) loading dose on Day 1, followed by 1.5 mg/kg IV (not to exceed 100 mg) daily dose for at least 14 days after the last positive culture.

The clinical study report for study A8851008 was submitted to fulfill the outstanding deferred pediatric PMR 311-1: *Deferred pediatric study under PREA for the treatment of candidemia and other forms of Candida infections (intra-abdominal abscess and peritonitis) in pediatric patients ages, zero months to 16 years of age.* On May 7, 2014, the Applicant received a waiver to study neonates (birth to 1-month-old) in Study A8851008.

In addition, a prior approval labeling supplement NDA (S-029) to add a warning regarding the use of anidulafungin in patients with hereditary fructose intolerance is discussed in Section 13.1.2.

[1] Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guidelines for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 62(4):e1-50.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Benefit-Risk Summary and Assessment

Anidulafungin (ERAXIS®) is approved for the treatment of candidemia and other *Candida* infections (intra-abdominal abscess and peritonitis) and esophageal candidiasis in adults. In this supplemental NDA (sNDA), the Applicant is seeking an indication for anidulafungin for treatment of candidemia and other forms of invasive *Candida* infections (intra-abdominal abscess and peritonitis) in pediatric patients, ≥ 1 month to 17 years of age. Neonates were not enrolled because the dosage of anidulafungin required for treatment of disseminated disease in the central nervous system (meningoencephalitis) has not been established. Furthermore, higher doses of anidulafungin would also increase exposure to the inactive excipient, polysorbate 80, to potentially toxic levels.

Candidemia/invasive candidiasis is a life-threatening infection which occurs in immunocompetent and immunosuppressed adults and pediatric patients. More than 90% of cases of invasive candidiasis are caused by five species, i.e., *Candida albicans*, *C. glabrata, C. tropicalis, C. krusei, and C. parapsilosis*. The pathogenesis and clinical course of the disease are thought to be similar between adult and pediatric patients with candidemia except for neonates, in whom higher rate of CNS dissemination is observed. The pediatric development plan included a determination of the anidulafungin dosage that achieved exposures in pediatric patients similar to that of adults, i.e., efficacy extrapolation based on matching drug exposures and an assessment of the safety of anidulafungin.

The Applicant conducted an open-label, noncomparative study, A8851008, to evaluate the safety and efficacy of anidulafungin in 68 pediatric patients (1 month to 17 years of age) with invasive candidiasis (> 95% of patients had candidemia). The most frequently reported risk factors for *Candida* infection were the use of broad-spectrum antibacterial drugs and presence of a central venous catheter (78%) followed by total parenteral nutrition (45%). All three age cohorts, 1 month to < 2 years (n=19), 2 to < 5 years (n=19) and 5 to < 18 years (n=30), received the same dose of anidulafungin IV, i.e. 3 mg/kg loading dose x 1 followed by 1.5 mg/kg per day. The median duration of anidulafungin treatment in the safety population was 11 days. Thirty-one (46%) patients were switched to receive follow-on treatment with oral fluconazole for a median of 8 days.

Safety was the primary endpoint in the study. Safety was evaluated through assessment of adverse events and monitoring of clinical laboratory tests (hematology and serum chemistry), vital signs, and physical examinations. Eleven patients (16%) died, with eight deaths occurring during the study and three deaths occurring outside the safety-reporting period. No deaths were attributed to anidulafungin. Treatment-emergent adverse events (TEAEs) were reported in 66 (97%) patients. Common TEAEs included vomiting (24%), diarrhea (22%), pyrexia (19%), elevated aminotransferases (19 %). Vomiting, diarrhea, generalized pruritus, and increased transaminases were considered treatment-related and led to

the discontinuation of anidulafungin in 6 patients (9%). Hepatobiliary adverse events occurred in 16 (23%) patients. Postbaseline increases in ALT levels to > 3x ULN were observed in 18 (29%) patients and elevated bilirubin ≥ 2x ULN in 10 (15%) patients. Among subjects with ALT in the normal range at baseline, maximum post baseline ALT elevations (>3 to 20x ULN) were observed in six patients (10%). Three patients fulfilled the biochemical criteria for Hy's Law; however, there was no progression to serious liver injury associated with anidulafungin. All postbaseline abnormalities in aminotransferases resolved to baseline levels or the normal range except for one patient who had elevated aminotransferases at the time of death related to progression of medulloblastoma. TEAEs were consistent with the known safety profile of anidulafungin and other echinocandins in clinical use and were consistent with the population of critically ill pediatric patients under study.

Efficacy was a secondary endpoint. Four patients were excluded from the efficacy analyses because they did not have a microbiologically-confirmed *Candida* infection. A successful global response required both a clinical response of success (cure or improvement) and microbiological response of success (eradication or presumed eradication). Global response at the end of IV therapy (EOIVT) was 70.6% and was similar to the global response rate at EOIVT (75.6%) reported in the adult anidulafungin invasive candidiasis trial VER002-9.

In summary, the safety findings for anidulafungin in pediatric patients (1 month of age and older) in study A8851008 were consistent with the known safety profile of anidulafungin and the echinocandin drug class. No new safety concerns were identified. An adequate and well-controlled trial (VER002-9) of anidulafungin for treatment of invasive candidiasis in adults supports the use of anidulafungin for the treatment of candidemia and other *Candida* infections (peritonitis and abdominal abscess) in pediatric patients as the pathogenesis of candidemia/invasive candidiasis is similar in adults and pediatric patients (1 month of age and older) allowing for the extrapolation of efficacy based on comparable drug exposure. Comparable global response rates at the EOIVT in study A8851008 provide supportive evidence for anidulafungin's efficacy in pediatric patients with candidemia/invasive candidiasis. Based on the analysis of the pharmacokinetic (PK) data, the proposed regimen of 3mg/kg IV loading dose followed by 1.5 mg/kg IV daily maintenance dose in pediatric patients 1 month to < 18 years of age achieves exposures comparable to that of adults treated with 200 mg IV loading dose followed by 100 mg IV daily maintenance dose. The steady-state PK exposures across the age groups were generally within the range of those in adults.

In the NDA prior approval labeling supplement (S-029), the Applicant included a warning regarding the use of ERAXIS (contains fructose) in patients with hereditary fructose intolerance (HFI). The clinical reviewers concluded that use of ERAXIS should be contraindicated in patients with known or suspected HFI because there is a risk of precipitating a metabolic crisis in these patients. In addition, careful history of HFI symptoms (nausea, vomiting, abdominal pain) with fructose/sucrose exposure should be obtained prior to ERAXIS administration because a diagnosis of HFI may not yet be established in pediatric patients.

1.3. Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Candidemia and other forms of invasive candidiasis are life-threatening infections and a major cause of mortality and morbidity in adult and pediatric patients. • The pathogenesis and clinical course of invasive candidiasis is similar in adult and pediatric patients except for pediatric patients less than 1 month old because invasive candidiasis in these patients is associated with a high incidence of disseminated disease and CNS disease, *Candida* meningoencephalitis.	Candidemia and other forms of invasive candidiasis are serious diseases with a significant mortality risk.
Current Treatment Options	• Treatment options for candidemia/invasive candidiasis in the 2016 IDSA clinical practice guidelines include an echinocandin (caspofungin, micafungin, anidulafungin), fluconazole, amphotericin B deoxycholate, lipid formulations of amphotericin B, and voriconazole.[1] Both caspofungin (Cancidas)[2] and micafungin (Mycamine)[3] are approved for the treatment of candidemia/invasive candidiasis in pediatric patients. • Nonclinical infection models indicate that higher doses of anidulafungin are needed to achieve adequate exposure	Anidulafungin should not be used to treat invasive candidiasis in pediatric patients less than 1 month old because of the high incidence of *Candida* dissemination and meningoencephalitis in this age group. Anidulafungin should not be used to treat osteomyelitis, endocarditis or meningitis.

[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021227s039lbl.pdf
[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021506s023lbl.pdf

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>in the central nervous system. The dosage of ERAXIS for the treatment of Candida dissemination into the CNS and the eye in humans has not been established.

• Anidulafungin has not been studied in osteomyelitis, endocarditis or meningitis.</td><td></td></tr>
<tr><td>Benefit</td><td>• Anidulafungin was evaluated in an open-label trial in pediatric patients (1 month to 17 years of age) with candidemia/ invasive candidiasis (study A8851008).
• Efficacy was a secondary endpoint. The global response rates at all time points were favorable and generally consistent with the results of the pivotal trial of anidulafungin for candidemia/invasive candidiasis (intra-abdominal abscess and peritonitis) in adults, VER002-9.
<table>
<tr><th>Time Point</th><th>Pediatric Study A8851008 (n=64)</th><th>Adult Study VER002-9 (n=127)</th></tr>
<tr><td>EOIVT</td><td>45 (70.3)</td><td>96 (75.6)</td></tr>
<tr><td>EOT</td><td>46 (71.9)</td><td>94 (74.0)</td></tr>
<tr><td>2- week follow-up</td><td>46 (71.9)</td><td>82 (64.6)</td></tr>
<tr><td>6- week follow-up</td><td>43 (67.2)</td><td>71 (55.9)</td></tr>
</table>
• The limitations of this pediatric trial are the open-label non-comparative design and the relatively small study population.</td><td>Efficacy of anidulafungin in the treatment of candidemia / invasive candidiasis in pediatric patients, 1 month of age and older is supported by an adequate and well controlled trial in adults and additional PK, safety and outcome data in pediatric patients.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Safety was the primary endpoint in this pediatric study. Common TEAEs included vomiting (24%), diarrhea (22%), and elevated aminotransferases (19%). • The frequencies of hepatobiliary adverse reactions reported with anidulafungin in pediatric patients (23.5%) were similar in adult patients (24.4%) in a phase 3 trial of candidemia/invasive candidiasis. • Infusion reactions were identified in 5 (7.4%) patients and included skin erythema, periorbital edema, and generalized pruritus. • ERAXIS contains polysorbate 80, an inactive ingredient. Life-threatening toxicities related to polysorbates have been reported in low-birth weight infants receiving medications with high levels of polysorbates. There are no reports of polysorbate toxicity associated with ERAXIS in pediatric patients.	The safety profile of anidulafungin in pediatric patients is similar to the safety profile of anidulafungin in adults and the echinocandin drug class in general. The rate of hepatobiliary adverse reactions a and hepatic test abnormalities in pediatric patients older than 1 month of age do not change the risk/benefit of anidulafungin for treatment of candidemia/invasive candidiasis. The current warning in labeling about hepatic adverse reactions and monitoring of hepatic laboratory tests during treatment is adequate. The infusion rate should not exceed 1.1 mg/min to avoid increase in the rate of infusion reactions as per the ERAXIS USPI. Anidulafungin exhibits an acceptable safety profile for treatment of candidemia/invasive candidiasis in pediatric patients, 1 month to 17 years of age. Candidemia/invasive candidiasis in pediatric patients younger than 1 month of age has a higher rate of central nervous system (CNS) and multi-organ dissemination than in older

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		patients. Dosage, safety and efficacy of anidulafungin in neonates (birth up to 1 month of age) has not been established. In addition, use of anidulafungin in patients younger than 1 month of age carries a potential risk of life-threatening toxicity associated with high doses of polysorbate 80, an inactive ingredient. The proposed labeling adequately conveys the safety risks. A REMS is not required.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data were not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Invasive *Candida* infections are life-threatening and one of the most important causes of nosocomial infections among pediatric patients.[4] *Candida* species are the second most common cause, behind coagulase negative staphylococci, of central line-associated bloodstream infections among hospitalized adult and pediatric patients in the United States. Incidence rates vary according to study design and range from 0.06 to 0.28 per 1000 inpatient days for pediatric patients, 0 to 17 years of age.[5,6] An incidence of 0.81 per 1000 admissions was reported in a pediatric prospective surveillance study.[7] Risk factors include the presence of a central IV catheter, broad spectrum antibacterial drugs, prematurity, total parenteral nutrition, abdominal surgery, and neutropenia/ immunosuppression.[6,8] Invasive *Candida* infections have a similar pathophysiology in adult and pediatric patients except that disseminated disease and *Candida* meningoencephalitis are more common in neonates (birth to 1 month). More than 90% of invasive disease is caused by the five pathogens, *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei. Most* infections caused by *Candida* species in the pediatric population are caused by *C. albicans or C. parapsilosis,* while the more antifungal-resistant species such as *C. glabrata, C. krusei, and C. auris* are less prevalent in pediatric patients in comparison to adults.[9, 10, 11] All-cause mortality for candidemia in pediatrics exceeds 15% in the

[4] Wisplinghoff H, Seifert H, Tallent SM, et al. Nosocomial bloodstream infections in pediatric patients in United States hospitals: epidemiology, clinical features and susceptibilities. Pediatr Infect Dis J. 2003;22:686–691.
[5] Dutta A, Palazzi DL. Candida non-albicans versus *Candida albicans* fungemia in the non-neonatal pediatric population. Pediatr Infect Dis J. 2011;30:664–668.
[6] MacDonald L, Baker C, Chenoweth C. Risk factors for candidemia in a children's hospital. Clin Infect Dis. 1998;26:642–645.
[7] Santolaya ME, Alvarado T, Queiroz-Telles F, et al.; Latin American Invasive Mycosis Network. Active surveillance of candidemia in children from Latin America: a key requirement for improving disease outcome. Pediatr Infect Dis J. 2014;33:e40–e44
[8] Zaoutis TE, Prasad PA, Russell Localio A, et al. Risk factors and predictors for candidemia in pediatric intensive care unit patients: implications for prevention. Clin Infect Dis 2010 Sep 1;51(5):e38-45.
[9] Arendrup MC, Dzajic E, Jensen RH, et al. Epidemiological changes with potential implication for antifungal prescription recommendations for fungaemia: data from a nationwide fungaemia surveillance programme. Clin Microbiol Infect 2013;19:e343–53.
[10] Palazzi DL, Arrieta A, Castagnola E, et al. Candida speciation, antifungal treatment and adverse events in pediatric invasive candidiasis: results from 441 infections in a prospective, multi-national study. Pediatr Infect Dis J 2014;33:1294–6.
[11] Warris A. *Candida auris*, what do pediatricians need to know? Arch Dis Child2018;103(9):891-894.

United States versus 6% for the matched patients without candidemia.[12,13] In addition to high rates of mortality, candidemia frequently results in severe morbidities including poor long-term neurodevelopmental outcomes.[14]

2.2. Analysis of Current Treatment Options

Antifungal drugs that can be administered intravenously for treatment of Candidemia and other forms of invasive *Candida* infections are summarized in Table 2-1.

Table 2-1 Summary of Treatment Armamentarium for Candidemia and Other invasive *Candida* Infections

Product (s) Name	Indication: Candidemia and other invasive *Candida* Infections	Year of Approval	Adult Dose (IV dosage)	Pediatric Dose (IV)	Comments
Caspofungin	Y	2001	Single 70-mg loading dose on Day 1, followed by 50 mg IV once daily	NA	-
Micafungin	Y	2005	100 mg IV daily	2 mg / kg/ IV daily *(age ≥4 months)*	Peds pts without HCME
Anidulafungin	Y	2006	Single 200 mg loading dose on Day 1, followed by 100 mg IV daily	NA	-
Amphotericin B formulations	Y		AMBisome: 3 to 5 mg / kg daily		Dosage differs by formulation
Fluconazole	Y	1990	200 mg to 400 mg IV daily	3 to 12 mg/ kg IV	Doses > 600 mg per day not recommended.
Voriconazole	Y	2002	6 mg/kg IV Q12h on day 1, then 3 to 4 mg / kg IV Q12h.		Non-neutropenic patients
Off-Label Use					
Posaconazole	N	2006	-	-	Approved for oropharyngeal candidiasis
Isavuconazonium sulfate	N	2015	-	-	No indications for *Candida infections*

[12] Zaoutis TE, Argon J, Chu J, et al. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. Clin Infect Dis. 2005;41:1232–1239.
[13] Pappas PG, Rex JH, Lee J, *et al*. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis 2003;37:634–43.
[14] Benjamin DK Jr, Poole C, Steinbach, WJ et al. Neonatal candidemia and end-organ damage: a critical appraisal of the literature using meta-analytic techniques. Pediatrics 112, 634–640 (2003).

Product (s) Name	Indication: Candidemia and other invasive *Candida* Infections	Year of Approval	Adult Dose (IV dosage)	Pediatric Dose (IV)	Comments
Itraconazole	N	1992	-	-	No indications *for Candida infections*

Source: Table constructed by the clinical reviewer.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

ERAXIS (anidulafungin) for injection, for intravenous (IV) infusion[15] was approved in the United States on February 17, 2006, for the treatment of candidemia and other forms of *Candida* infections (intra-abdominal abscess, and peritonitis) and esophageal candidiasis in adults. Anidulafungin is approved in 96 countries and is currently marketed in 83 countries worldwide. It is estimated that since the product was first approved (February 17, 2006 through January 31, 2019), 194,027 patients (69771 males and 124256 females) have been exposed in the United States, and 832,745 patients worldwide.[16]

3.2. Summary of Submission Regulatory Activity

At the time of original NDA approval, the Applicant agreed to conduct a pediatric study. The study was required under the Pediatric Research Equity Act (PREA) and was listed in the February 17, 2006, approval letter as a deferred required postmarketing study commitment (PMR 311-1). The study, "Deferred pediatric study under PREA for the treatment of candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in pediatric patients ages zero months to sixteen years of age," had an agreed to February 17, 2011, final study report submission due date.

On December 21, 2007, under IND 054597, the Applicant submitted new clinical protocol (A8851008) entitled, "A prospective, open-label study to assess the pharmacokinetics, safety and efficacy of anidulafungin when use to treat children with invasive candidiasis, including candidemia" to address PMR 311-1. This study intended to evaluate the pediatric patients age 1 month to 18 years old.

On November 8, 2010, the Applicant submitted a request for an extension of the Final Report Submission date due to slow study enrollment. A Revised Milestone letter to extend the Final

[15] ERAXIS® USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021632s026lbl.pdf
[16] ERAXIS. Development Safety Update Report, February 1, 2018, submitted March 27, 2019.

Report Submission date from the February 2011 to November 30, 2013 was issued to the Applicant on December 17, 2010.

Additionally, the Applicant submitted deferral requests on May 23, 2013 and September 3, 2015. Both requests were granted. Finally, the September 3, 2015, request extended the Final Report Submission date to November 29, 2019.

A waiver to study neonates 0 to 1 month of age due to the potential toxicity in neonates related to polysorbate 80, an inactive ingredient in ERAXIS, was communicated to the Applicant on May 7, 2014.

The Applicant submitted the Final Report for Clinical Study A8851008 under Supplement 27 to NDA 021632 on November 22, 2019, to fulfill the outstanding deferred PREA PMR 311-1.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical site inspections were not considered necessary for this sNDA.

4.2. Product Quality

No new product quality information was included in the sNDA.

4.3. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

A Pharmacology/Toxicology review was completed for several nonclinical studies submitted to this sNDA including a distribution study in neonatal rats, range-finding and definitive juvenile toxicology studies in rats with anidulafungin as a sole test article, and range-finding and definitive juvenile toxicology studies in rats with anidulafungin in combination with voriconazole (Study Nos. PF-03910960/13AUG09/101709, LIA00527, and 10GR127 respectively). A review of the published literature conducted by the Applicant did not identify any relevant nonclinical publications with anidulafungin. Pharmacology/Toxicology has no objection to the approval of this sNDA.

5.2. Referenced NDAs, BLAs, DMFs

The study summary and review information regarding the submitted nonclinical pharmacology and toxicology studies for the initial application and approval of ERAXIS can be found in the Pharmacology/Toxicology NDA Review and Evaluation for NDA 021632 by Owen McMaster, Ph.D. in DARRTS (11/22/2005).

5.3. ADME/PK

Type of Study	**Major Findings**
Distribution	
Distribution Of Anidulafungin (PF-03910960) Into Bone, Brain, And Heart Tissues Of Neonatal Rats (PF-03910960/13AUG09/101709)	Following a single SC dose, brain concentrations were lower than plasma. By day five of repeated SC dosing, brain concentrations were similar to plasma levels. Bone concentrations were similar to plasma concentrations at all time points. Heart concentrations were generally higher (<2-fold) relative to plasma. In plasma, bone, and brain, exposures increased slightly (<2-fold) with daily dosing for 5 days.]

Type of Study	Major Findings
TK data from general toxicology studies *Juvenile Toxicology Study* *Subcutaneous Repeat-Dose Toxicity Study of PF-03910960 in Neonatal Rats, Study No. LIA00527*	Rat (Study No. LIA00527) $T_{1/2}$: Not calculated. Accumulation: Plasma C_{max} were 0.8-fold at the end of the dosing period of the C_{max} at the beginning of the dosing period for the doses tested. The AUC_{0-24} were 1.3-1.6-fold higher from beginning to end of dosing. Dose proportionality: Anidulafungin exposure increased in a roughly dose-proportional manner.
Juvenile Toxicology Study *Combination Subcutaneous and Oral (Gavage) Repeat Dose Toxicity Study of PF-03910960 and UK-109,496 in Juvenile Rats, Study No. 10GR127*	Rat (Study No. 10GR127) *Anidulafungin* $T_{1/2}$: Not calculated Accumulation: AUC_{0-24} was approximately 1.5-times higher on day 56 compared to day 21 for the same 30 mg/mg dose. *Voriconazole:* Accumulation: Change in AUC_{0-24} was approximately 0.8-0.9-times the beginning at the end of dosing for groups dosed with 10 mg/kg and 1.7-times the beginning AUC_{0-24} at the end of dosing for the group dosed with 3 mg/kg *Interaction:* No large changes in AUC_{0-24}, C_{max} or T_{max} were apparent in either drug with concomitant dosing compared to dosing of the drugs separately.

5.4. Toxicology

5.4.1. General Toxicology

The Sponsor submitted several dose-range finding and definitive studies with anidulafungin alone and in combination with oral voriconazole administered subcutaneously to juvenile rats. All of the juvenile toxicity studies focused primarily on liver toxicity. No juvenile specific toxicities or any increases in sensitivity were reported.

Study title/ number: Subcutaneous Repeat-Dose Toxicity Study of PF-03910960 *[anidulafungin]* in Neonatal Rats / Study No. LIA00527 *[definitive study]*

- The study was designed to focus on changes in juvenile animal liver sensitivity to anidulafungin.
- A reduction in red cell mass in the MD and HD males and HD females was observed, which is indicative of regeneration anemia, a finding similar to those seen in adult animals with repeat dosing.

- Liver weights increased in HD animals, which did not fully resolve by the end of the recovery period, but no histopathological or clinical chemistry correlates were reported.
- Increase in neutrophils in MD and HD groups, decreased albumin, increased globin and decreased A:G ratio in HD group are findings that are consistent with low level inflammation.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	Once daily: vehicle control, 3 (LD), 10 (MD), or 30 (HD) mg/kg/day
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	Drug concentrate (100 mg/30 mL): 1% fructose, 5% mannitol, 2.5% polysorbate 80, 0.112% tartaric acid in water Diluent: 5% dextrose
Species/Strain:	Rat (b) (4)
Number/Sex/Group:	Main study: 10/sex/dose Recovery study: 10/sex/dose
Age:	Post-natal day (PND) 4
Satellite groups/ unique design:	Toxicokinetics: 18/sex/dose Recovery Study animals were dosed identical to the Main Study animals, then maintained without dosing until necropsy on PND 97 Histopathological examination was only conducted on liver and any gross lesions found in situ were collected at necropsy.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No anidulafungin-related deaths occurred in the study.
Clinical Signs	No anidulafungin-related clinical signs were observed.

Body Weights	Body weight gains were statistically lower in main and recovery group male rats compared to controls during PND 22-29. Mean body weight in 10 and 30 mg/kg dose groups was also decreased compared to controls (6-15% lower than controls). Final body weights were 93%, 94%, 92% in the 3, 10 and 30 mg/kg dose groups compared to concurrent controls on PND 57. During the recovery period, mean body weight gain and overall body weight were comparable to controls in all dose groups. Female animals in the 30 mg/kg dose group gained less body weight between PND 8 and 29 compared to control which was statistically significant between PND 22-29, after which they were comparable or exceeded controls. The average body weights were 99%, 98%, and 99% of the concurrent controls on PND 63, for the 5, 10 and 30 mg/kg dose group respectively.
Hematology	Dose dependent decreases (6-19%) in hematocrit, red blood cell counts, hemoglobin were observed in MD and HD males and HD females. Neutrophil counts were increased in the MD and HD groups and monocyte counts were increased in the HD females, which might suggest nonspecific inflammation.
Clinical Chemistry	Albumin levels were lower (14-16%) and globin levels higher (12-14%) (with a corresponding change in A:G ratio (25-27%)) in the HD group compared to the control. The minor change is consistent with an acute phase response to increased inflammation noted in the hematological parameters. Serum glucose was decreased in the HD groups at the end of dosing (16-18%) and serum cholesterol increased (11-13%).
Gross Pathology	No treatment-related in situ gross pathology findings were reported.
Organ Weights	Only the livers were collected and weighed. HD male relative liver weights were increased 15%. HD female absolute and relative liver weights were increased (31-33%) and MD female relative weights were increased (6-9%). Recovery animal absolute and relative liver weights were still significantly increased in HD females (12-14%).
Histopathology Adequate battery: No (limited tissues evaluated)	Only liver was evaluated microscopically. No anidulafungin-related histopathological findings were reported in the liver.
***[Other Evaluations]* Neurobehavioral Assessment**	Motor activity (PND 79) and learning and retention of a spatial navigation task (water-filled Morris maze) was tested between PNDs 80 and 89. There were no findings in treated animals different from controls.

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.
*: *[if the answer is "no" explain why the histopath battery is not adequate]*

Study title/ number: Combination Subcutaneous and Oral (Gavage) Repeat Dose Toxicity Study of PF-03910960 *[anidulafungin]* and UK-109,496 *[voriconazole]* in Juvenile Rats /Study No. 10GR127 *[definitive study]*

- Study was only designed to evaluate juvenile liver toxicity and to evaluate the toxicokinetics of both drugs.

- Treatment-related findings in body weight (reduced body weight gain), hematology (decreased red cell mass, change in leukocytes), clinical chemistry (albumin, globin and A:G ratio changes), and organ weights (increased liver weight) were similar for anidulafungin groups to those seen in the juvenile toxicology study of anidulafungin alone. Minimal single cell necrosis was observed in liver histopathology in groups dosed with both anidulafungin and voriconazole.
- Toxicokinetics for anidulafungin and voriconazole were not significantly different with co-administration.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	Anidulafungin/voriconazole (mg/kg/day) Group 1: 0/0 Group 2: 30/- Group 3: -/10 Group 4: 30/3 Group 5: 30/10 PND 21-56, daily
Route of administration:	Subcutaneous injection (anidulafungin); Oral gavage (voriconazole)
Formulation/Vehicle:	Anidulafungin: 1 % fructose, 5% mannitol, 2.5% polysorbate 80, 0.112% tartaric acid in water, pH of (b) (4). in 5% dextrose Voriconazole: (b) (4)
Species/Strain:	Rat (b) (4)
Number/Sex/Group:	Main study: 10/sex/group
Age:	Starting at PND 21 (juvenile)
Satellite groups/ unique design:	Recovery: 10/sex/group Toxicokinetics: 18/sex/group
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No test-article related deaths were reported.

Parameters	Major findings
Clinical Signs	No test-article related clinical observations were reported.
Body Weights	No changes in body weights or body weight gains were found with administration of anidulafungin or voriconazole as a single agent. Average body weights were reduced approximately 10% in group 4 and group 5 males cumulatively and for most of time intervals and terminal body weights were statistically significantly lower in groups 2, 4, and 5 (8-10%). Females in groups 4 and 5 had transient reduced body weight gains but no statistically significant differences in terminal body weights between groups.
Hematology	Male and female rats in groups 2, 4, and 5, dosed with anidulafungin without or with voriconazole had a 6-11% reduction in red cell mass (RBC, HGB, and HCT). Platelet counts increased (26-60%) in males and females in groups 2, 4, and 5, however clotting parameters were not tested. Leukocyte increases (32-46%) were observed with increases in neutrophil (124-149%) and monocyte (64-93%) counts in males and females and increases in eosinophils (38-48%) and basophils (37-53%) in female animals in the same groups. Reticulocyte counts were decreased in the end of the recovery period in male and female rats in groups 2, 4, and 5 (13-21%) compared to controls (group 1).
Clinical Chemistry	An increase in globin (15-21%) and corresponding decrease in albumin: globin ratio was observed in males in groups 2, 4 and 5 (15-21% and 23-28%, respectively for globin and A:G ratio) and females in groups 4 and 5 (15-16% and 21-28%, respectively). Cholesterol levels were increased in male rats in groups 2, 4, and 5 (24-31%) and female rats in groups 4 and 5 (13-16%). In female rats GGT was increased in groups 3 and 5, when voriconazole was administered at 10 mg/kg (86-93%). There were no differences between groups at the end of the recovery period.
Gross Pathology	No test-article related gross pathologies were reported.

Parameters	Major findings
Organ Weights	At necropsy liver, prostate, epididymides, seminal vesicle gland, ovaries, testes and uterus were weighed. At the end of dosing liver weights were increased in groups 2, 4, and 5 compared to group 1 rats, in male rats (absolute 1-8% and relative to BW 9-19%) and female rats in (absolute 16-21% and relative 19-30%), when dosed with anidulafungin. During the recovery period, the relative liver weights in groups 2, 4, and 5 males (8-11%), and group 2 females (6-8%) remained elevated compared to controls but the differences were less in magnitude in both sexes compared to the end of the dosing period. There was a statistically significant decrease (18-36%) in the absolute and relative weights of epididymis at the end of the dosing period in animals receiving anidulafungin alone or in combination with voriconazole that was not found after the recovery period (Day 84).
Histopathology Adequate battery: No	Histopathology was performed only on liver. In males and females in groups 4 and 5, an increase over group 1 in incidence of minimal single cell necrosis in the liver was reported, with a dose related increase.
[Other evaluations-sexual maturity]	No test article related findings were reported; however, few of the animals were included in this observation.

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.
*: *[if the answer is "no" explain why the histopath battery is not adequate]*

General toxicology; additional studies

Preliminary range-finding juvenile toxicology studies and a study to compare toxicokinetics of anidulafungin with different routes of administration were conducted in support of this submission and to inform dose setting for the juvenile studies described above.

Study title/ number: Intravenous, Subcutaneous or Intraperitoneal Dosage-Range Single Dose Toxicity Study of PF-03910960 in Neonatal Rats/Study No. 09GR029

Methods

Age at dosing start: PND 7
Pups in main study: 3 pups per sex per litter per dose of administration of which 2 pups/sex/dose were used in the TK and tissue collection and 1 pup/sex/dose were kept in a 7-day recovery group.
Dosing regimen: subcutaneous, intravenous (slow bolus), or intraperitoneal
Doses: 30, 75, 100 mg/kg/day (no control group)
GLP: No

Evaluated were viability, clinical observations, body weight, toxicokinetics and necropsy.

Results
No mortality or clinical signs other than related to the route of administration were noted. In the intravenous dose group, body weight gains were reduced in the 100 mg/kg dose compared to the 30 and 75 mg/kg doses, which continued into the recovery period (note the recovery group was one male and one female pup).

The IV and SC routes of administration had dose proportional increases in exposure between the 30 and 75 mg/kg doses, with little increase to the 100 mg/kg doses. The IV route had higher C_{max} than the SC or IP routes. C_{max} resulting from IV, SC and, IP administration for 30 mg/kg were calculated to be 41, 15.7, and 9.3 mcg/mL, for 75 mg/kg rats 215, 39.6, and 43.8 mcg/mL, and for 100 mg/kg rats >1000, 45.6, and 36 mcg/mL, respectively. AUC_{0-24} resulting from IV, SC and, IP administration for 30 mg/kg were calculated to be 364, 279, and 151 mcg*hr/mL, for 75 mg/kg 1,230, 705, and 762 mcg*hr/mL, and for 100 mg/kg (not reported), 847, and 495 mcg*hr/mL, respectively. C_{max} and AUC_{0-24} were significantly lower with SC administration compared to IV administration. The TK values for all methods were also lower than those reported in for comparable dose levels in adult rats administered 20-minute infusions (see Pharmacology/Toxicology review of NDA 21632 by Dr. Owen McMaster, in DARRTS dated 11/22/2005.)

Study title/ number: Subcutaneous Dosage-Range Repeat-Dose Toxicity Study of PF-03910960 in Neonatal Rats/Study No. LIA00544

Methods
Age at dosing: PND 4-28
Pups in main study: 16 males, 16 females
Pups in satellite TK study: 16 males, 16 females
Dosing regimen: subcutaneous, daily
Doses: 0, 10, 30, or 60 mg/kg/day
GLP: No

Blood for TK measurements were collected on PND 4 and PND 28 at 0.167, 1, 6, and 24 hours after dosing. One pup per group was bled for each timepoint on PND 4 and 2 pups per group from the main study were used for each time point on PND 28.
After terminal blood sample collection, heart, brain, and bone were collected from pups in the 0 and 10 mg/kg dose group to measure tissue levels of the test article.
Hematology and clinical chemistry were performed on serum or whole blood samples on PND 28 or 29 in the main study. A gross necropsy was performed in situ, and the liver was weighed and preserved for further evaluation by histochemistry. No other tissues were collected for histopathological evaluation.

Results

Body weight gains and mean body weights were reduced at doses 30 mg/kg and above for the dosing period. Gross lesions of the liver were found in female pups in a dose dependent manner, but it was unclear if the lesion were test article related because of the limited number of pups. The lesions were not seen in male pups. No effects were found on liver weights and no significant changes in serum chemistry were observed.

Toxicokinetic parameters:
T_{max} (all groups): 6 hours, except in 10 mg/kg dose group on PND 4 where it was 1 h
Exposure increased in a dose-dependent manner.
At the highest dose group C_{max} and AUC_{0-24} were lower on PND 28 than PND 4, which is of unclear significance due to the limited number of samples. Following a singe 10 mg/kg dose, anidulafungin was detected in all tissues tested, namely blood, brain, bone and heart. The relative C_{max} was heart>plasma≈bone>brain for PND 4 pups. AUC_{0-24} followed the same pattern.

Study title/ number: Combination Subcutaneous and Oral (Gavage) Dosage-Range Repeat Dose Toxicity Study of PF-03910960 [*anidulafungin]*and UK-109,496 [*voriconazole*] in Juvenile Rats/Study No. 10GR016

Methods
Age at dosing: PND 21-34
Pups in main study: 18 litters of 5 males, 18 litters of 5 females
Dosing regimen: anidulafungin: subcutaneous, daily; voriconazole oral (gavage) daily
Doses (anidulafungin/voriconazole, mg/kg):

Group 1: 0/0
Group 2: 30/3
Group 3: 30/10
Group 4: 30/50
Group 5: 0/50

GLP: No

Data collected were viability, clinical observations, body weights and body weight changes, toxicokinetics, and necropsy observations. Toxicokinetic samples were taken at 1, 3, 6, and 24 hours post-dose on post-natal day (PND) 21 and PND 34. For male rats, organs/tissues collected and weighed at necropsy were the prostate, testes, epididymides, vas deferens, seminal vesicles (with fluid) and liver and these tissues were retained for possible histological evaluation. For female rats, organs/tissues collected and weighed at necropsy were the ovaries and oviducts, uterus with cervix, vagina and liver were collected. These were retained for possible future evaluation. No histopathological examination of any tissues was conducted.

Results
There were no unscheduled deaths or test-article associated clinical signs or gross lesions in any dose group. Body weight gains were reduced overall for the dosing period in male and female

rats in group 4 compared to control. Body weight gains overall for group 4 were 87% and 82% for male and female rats compared to controls. A net loss in body weight occurred in groups 4 and 5 in male and female rats on PNDs 21-22, and reduced body weight gains in these groups on PNDs 22-23. On PND 34/35 right and left testis weights were increased 18-19% in group 5, and in groups 3 and 4 the prostate weight was reduced 15 and 28%, respectively. In female rats on PND 34/35 the absolute and relative weights of the left and right ovary were reduced in group 4 (32%) and the uterus weight was reduced in groups 4 and 5 (30% and 10%, respectively). The significance of these changes in reproductive organ weights is unclear, particularly because tissues were not examined microscopically. Relative and absolute liver weights were increased (25-35% and 14%-28% respectively) in groups 4 and 5 compared to controls.

Anidulafungin exposure was similar on the two days of toxicokinetic testing and appeared similar across groups with different voriconazole doses. Voriconazole exposure did not appear markedly changed by co-administration of SC anidulafungin. Increased voriconazole dose led to greater than proportional increase in exposure to voriconazole. Voriconazole exposure tended to decrease from the first to last day of dosing, but still had a greater than proportional to dose relationship on the last day of dosing. Co-administration had no effect on any PK parameters for either drug.

6 Clinical Pharmacology

6.1. Executive Summary

In this sNDA, the Applicant seeks to update the ERAXIS (anidulafungin) USPI with a new population of pediatric patients, 1 month to <18 years of age, for the indication of treatment of candidemia and other invasive *Candida* (ICC) infections. The proposed pediatric dose is 3.0 mg/kg (not to exceed 200 mg) loading dose on Day 1, followed by 1.5 mg/kg (not to exceed 100 mg) as a once daily (QD) maintenance dose for at least 14 days after the last positive culture. The Applicant submitted data from two clinical studies and a population pharmacokinetic/pharmacodynamic (PK/PD) analysis:

- The Duke University Investigator Initiated Research Study (Duke IIR Study), a Phase 1 study of the PK of anidulafungin in infants and neonates.

- Study A8851008, a Phase 3b study in which pediatric subjects aged 1 month to <18 years with confirmed ICC (or at risk for ICC in the 1 month to <2 years age cohort) were treated with anidulafungin [conducted to fulfill the Pediatric Research Equity Act (PREA) Postmarket Requirement Number 311-1: Deferred pediatric study under PREA for the treatment of candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in pediatric patients ages zero months to sixteen years of age].

- The Population Modeling Analysis Report (PMAR): Pharmacokinetic- Pharmacodynamic Analysis of Anidulafungin in Pediatric and Adult Patients with Invasive Fungal Infections.

Based on a review of the studies submitted by the Applicant and also based on the modeling and simulation analyses performed by the Clinical Pharmacology review team, it is concluded that the proposed dosing regimen of 3.0 mg/kg loading dose followed by 1.5 mg/kg QD maintenance dose provides comparable exposures for pediatric patients ages 1 month to <18 years old compared to those in adults. The steady-state PK exposures across the age groups are generally within the range of those in adults. Thus, this proposed dosage regimen of ERAXIS in pediatric patients 1 month to <18 years of age with ICC is acceptable from a Clinical Pharmacology perspective.

No exposure-response (E-R) relationship has been established for the ICC indication in adult patients. Therefore, exploratory E-R analyses were performed based on the pediatric patients (n=62) from Study A8851008 (Refer to Section 17.3 for the detailed E-R analyses). In graphical examinations of the relationships between the exposure metrics ($AUC_{0\text{-}24,ss}$, and $AUC_{0\text{-}24,ss}$ /MIC) and the global response rate at EOVIT or EOT, no apparent trend of loss of efficacy was

observed at the lower exposures in the infant age group in A8851008. Furthermore, the global response at EOIVT by age groups was similar across the age groups in Study A8851008 (Refer to Section 7. Clinical Efficacy).

6.1.1. General Dosing and Therapeutic Individualization

Outstanding Issues

None

6.2. Comprehensive Clinical Pharmacology Review

6.2.1. General Pharmacology and Pharmacokinetic Characteristics

Duke IIR Study

The Duke IIR Study was a prospective, open-label, single center, pharmacokinetic study of anidulafungin in 15 infants and neonates less than 24 months of age at risk for candidemia and invasive candidiasis. Subjects received study drug for up to 5 days and were stratified by age, from 0-30 days (neonates) and >30 days to 2 years (infants). The median postnatal age, gestational age at birth, and birth weight of all subjects enrolled were 28 days (range; 2-451), 36 weeks (24-40), and 2090 g (660-3969), respectively. Subjects received anidulafungin 3 mg/kg loading dose on study day 1 and 1.5 mg/kg every 24 hours on study days 2-5. The dosage studied in these infants and neonates was extrapolated from studies in older children. Blood was collected to determine plasma concentrations of anidulafungin on Days 1 and 3 to 5. On Day 1, blood samples were collected at the end of the 1-hour infusion, 3 to 6, 8 to 12, and 18 to 24 hours from the start of the infusion. On day 5, blood samples were collected within two hours prior to the start of the anidulafungin infusion, at the end of the 1-hour infusion, 3 to 6, 8 to 12, and 18 to 24 hours from the start of the infusion. Additionally, samples at 48 and 72 hours after the last dose were obtained but did not exceed 9 total samples per patient. In order to minimize the amount of blood sampling, hematology and chemistry laboratory measures were obtained per local standard of care. The Day 5 sampling scheme could be completed on Day 3 or Day 4 if the infant or neonate received <5 days of therapy. If an infant weighed <1000 g at enrollment, and the acquisition of pharmacokinetic samples represented greater than minimal risk, then the Day 5 sampling was deferred.

The PK population was the subset of all subjects in the intent-to-treat (ITT) population who received anidulafungin on at least 3 days and who provided blood samples used to assess evaluable anidulafungin plasma samples. Fourteen subjects were included in the PK analysis.

Anidulafungin Pharmacokinetic Results

One hundred and nineteen (119) plasma concentrations were obtained from 14 subjects. Anidulafungin concentration-time profiles were similar between age cohorts. Pharmacokinetic

parameters (noncompartmental analysis) after the loading dose and multiple dosing are summarized in Table 6-1. After the loading dose, only observed maximum anidulafungin concentrations (Cmax LD) were obtained; other PK parameters were not calculated for the loading dose given insufficient number of samples.

Table 6-1. Summary of Anidulafungin Pharmacokinetic Parameters by Age Cohort

Age Cohort	Statistic	CL (L/kg/h)	Vss (L/kg)	AUCss (µg*h/mL)	Cmaxss (µg/mL)	Cmax LD (µg/mL)
Neonates (0-30 days)	N	8	8	8	8	5
	Mean	0.024	1.94	72.56	4.08	3.89
	CV%	47	72	34	35	44
Infants (>30 days to 2 years)	N	6	6	6	6	6
	Mean	0.016	1.12	120.98	6.71	7.79
	CV%	45	80	66	63	54
Total	N	14	14	14	14	11
	Mean	0.020	1.59	93.31	5.21	6.02
	CV%	50	78	62	60	62

Reviewer's Comments: The Cmax of anidulafungin in patients 1 month <2 years in this PK sub-study is comparable to the Cmax obtained from the population PK analysis presented below. The AUCss appears to be characterized by a higher variability (%CV ~66%) and is higher than the AUCss obtained from the population PK analysis.

Study A8851008

Study A8851008 was a prospective, open-label, non-comparative, multicenter, multinational study designed to assess the safety, efficacy, and PK of anidulafungin for the treatment of ICC in pediatric patients 1 month to <18 years of age.

Sufficient number of subjects were recruited to ensure there were approximately 60 evaluable subjects who received at least 1 dose of study drug and had confirmed *Candida* infection. Enrollment was stratified by age (1 month to <2 years, 2 to <5 years, and 5 to <18 years), allowing 20±2 subjects in each stratum.

The overall mean (standard deviation) age in the safety population was 5.83 (5.05) years; a greater number of subjects (n=30) were in the 5 to <18 years age group compared with the 1 month to <2 years (n=19) and 2 to <5 years age group (n=19). More males than females (38 versus 30 subjects) were enrolled. The majority of subjects were white (79.4%).

All subjects received IV anidulafungin as study drug. On Day 1, the subject received a loading dose of 3.0 mg/kg (not exceeding 200 mg) by IV administration at a rate of 1.1 mg/min or less.

The subject then received a once daily maintenance dose of 1.5 mg/kg (not exceeding 100 mg) from Day 2 onwards.

In the study report, there were two notable protocol deviations. First, in a total of 20 patients, the infusion was not at the protocol specified rate of 1.1 mg/min (reported to be as low as 0.28 mg/min and as high as 2 mg/min). In nine patients, the infusion rate exceeded the protocol specified rate of 1.1 mg/min (1.23 mg/min to 2 mg/min); a single infusion-related AE was reported. In ten patients, infusion time was up to 50% slower than recommended/calculated per protocol. In two patients, infusion rate on certain study days could not be determined due to the missing infusion stop time.

Second, due to varying interpretations of the dosing and administration instructions across study sites, the overfill volume was not removed from the pre-filled 100 mL IV bags during the course of dose preparation in 31 patients. Following a detailed assessment of the potential impact of the failure to remove overfill volume, the Applicant concluded the following:

1. Failure to remove the overfill volume could have resulted in a final drug concentration less than the target of 0.77 mg/mL (in the range of 0.71 to 0.77 mg/mL) leading to a potential for under-dosing (1 to 9% lower dose) of anidulafungin.
2. Given the known variability in anidulafungin exposure in adults and pediatric patients (AUC CV% in the range of 30 to 40%), this potential difference in dose would not be of a magnitude considered to be clinically impactful; therefore, the safety of trial subjects and scientific value of the study (i.e., safety and efficacy data) was not impacted by failure to remove overfill volume.

Review Team's Comments: We agree with the Applicant's conclusions regarding the overfill volume. The Cmax, which would be driven more by infusion rate and/or concentration of drug in the IV solution, across all pediatric ages is similar enough to that in adults (Table 6-6). In addition, the efficacy and safety of anidulafungin in pediatric patients in Study A8851008 was found to be acceptable and the Clinical Pharmacology review team could not find any relationship between PK exposure and response for efficacy. Thus, from a Clinical Pharmacology perspective, the infusion rate or overfill volume issues had no significant impact on the PK of anidulafungin.

PK Sub-Study

A PK sub-study was conducted in the first 6 children in the 1 month to <2 years age group who were enrolled at selected centers to confirm the appropriate dosage regimen of anidulafungin IV for this age group.

Following initiation of treatment, blood samples (approximately 0.3 to 0.5 mL each) were collected for anidulafungin measurement at 6 time points as follows:

- 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.

All Subjects (Excluding the PK Sub-Study)
For all other study subjects (excluding those in the PK sub-study), blood samples (approximately 0.3 to 0.5 mL each) for anidulafungin measurement were collected at 3 to 5 occasions during the study, at specified time points on Day 1 through Day 9.

- Day 1: Postdose (between 0 and 2 hours following the end of anidulafungin infusion).
- Day 3: Predose (just prior to the start of anidulafungin infusion).
- Day 5: Postdose (between 0 and 3 hours following the end of anidulafungin infusion).
- Day 7: Delayed postdose (between 6 and 12 hours following the end of anidulafungin infusion).
- Day 9: Predose (just prior to the start of anidulafungin infusion).

Bioanalytical Summary
Plasma samples were assayed for anidulafungin by use of a validated liquid chromatography tandem mass spectrometry method (PPD, Richmond, VA). The method was validated in the linear range from 0.05 to 20.0 µg/mL with an overall precision of over 95.9% and accuracy of 96.8-104.2%.

Reviewer's Comments: The bioanalytical assay is similar to the previously reported assay for anidulafungin and the validation parameters are acceptable. This study was not inspected by the Office of Study Integrity and Surveillance (OSIS) because the bioanalytical site was recently inspected.

The performance of the method during validation is summarized in the below Table 6-2.

Table 6-2. Summary of the Validated Analytical Method for Anidulafungin

Method Validation Report	Matrix/ Anticoagulant	Sensitivity (LLOQ-ng/mL)	Assay Range (ng/mL)	Inter-assay Precision %CV	Inter-assay Accuracy %RE	Clinical Protocol
A8859004	Human Plasma (Sodium/Lithium Heparin)	50.00	50.00-20,000.00	≤7.32	-4.33 to 0.0386	A8851008
A8859004 Addendum 1	Human Plasma (Sodium/Lithium Heparin)	50.00	50.00-20,000.00	≤7.28	-5.87 to 0.332	A8851008
A8859004 Addendum 2	Human Plasma (Sodium/Lithium Heparin)	50.00	50.00-20,000.00	≤11.7*	0.468 to 8.81*	A8851008

%CV=percent coefficient of variation; %RE=percent relative error/difference from theoritical; LLOQ=lower limit of quantification
*Intra-assay statistics

Plasma specimens were stored at approximately -70°C until analysis, and assayed within established stability data generated during validation (740 days at -20°C and 1597 days at -70°C). Calibration standard responses were linear over the range of 50.00 ng/mL to 20,000 ng/mL. Table 6-3 presents the summary of the assay performance in the A8851008 clinical study sample analysis reports.

Table 6-3. Summary of the Bioanalytical assay performance for Anidulafungin

Clinical Protocol	Matrix	Assay Range (ng/mL)	LLOQ (ng/mL)	Inter-assay Precision %CV	Inter-assay Accuracy %RE	ISR acceptance rate %
A8851008	Human Plasma/Lithium Heparin	50.00	50.00-20,000.00	≤9.71	-10.6 to 4.17	90.00
A8851008 Amendment 1	Human Plasma/Lithium Heparin	50.00	50.00-20,000.00	≤8.68	-10.6 to 4.17	90.00
%CV=percent coefficient of variation; %RE=percent relative error/difference from theoritical; ISR=Incurred Sample Reanalysis						

PK Results

The final PK sub-study dataset included 6 anidulafungin concentrations per subject plus 1 concentration prior to start of treatment. These data were obtained from the 6 subjects in the 1 month to <2 years age group who underwent intensive (serial) PK sampling.

Anidulafungin PK exposures in the 6 subjects in the PK sub-study fell within the expected range for adult ICC patients dosed with 200 mg load followed by 100 mg/day, which supports dose selection for the youngest age group.

A descriptive summary of anidulafungin PK parameters from these 6 subjects is presented in in Table 6-4.

Table 6-4. Summary of Anidulafungin PK Parameters in PK Sub-Study (First 6 Subjects in the 1 Month to <2 Year Age Group)

	AUC_{24} (ng.hr/ml)[a]	C_{max} (ng/ml)[b]	T_{max} (hr)	T_{last} (hr)
N	6	6	6	6
Geometric mean (CV%)	66449.1 (28)	5963.53 (29)	NA	NA
Median (range)	70190.3 (42940-87676)	6770.00 (3910.0-7720.0)	0.392 (0.17-2.25)	24.04 (23.7-24.4)

Abbreviations: AUC=area under the plasma concentration-time profile; AUC24=area under the plasma concentration-time profile from time 0 to the time of last quantifiable concentration; Cmax=maximum observed concentration; CV%=percent coefficient of variation; N=number of subjects at available for evaluation at time point; NA=not applicable; PK=pharmacokinetic; T_{last}=time of last quantifiable concentration; T_{max}=time for C_{max}
a. AUC was calculated based on the observed concentration data using the trapezoidal rule without any extrapolation. Where T_{last} is <24 hours, the actual AUC_{24} would be slightly higher than the reported value.
b. C_{max} was the maximum observed concentration without any extrapolation. Since flexible PK sampling was allowed, some study sites did not collect the PK sample immediately at the end of infusion. Therefore, it may not reflect the true peak concentration.

Reviewer's Comments: The Cmax and AUC24 of anidulafungin in this PK sub-study in patients 1 month - <2 years of age are comparable to those obtained from the population PK analysis presented below.

6.2.2. Clinical Pharmacology Questions

Does the proposed dosing regimen provide adequate exposure for pediatric patients for treatment of ICC?

The proposed dosing regimen provides comparable PK exposures for pediatric patients ages 1 month to <18 years old compared to those in adults. The model derived steady-state exposures ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$ and $C_{min,ss}$) in pediatric patients (DUKE IIR study and A8851008) are presented by age groups in Table 6-5. The geometric mean ratios (GMR) for $AUC_{0\text{-}24,ss}$, and $C_{min,ss}$ in the various pediatric age groups range from 0.90 to 0.98 compared to that of adults. $C_{max,ss}$ is slightly higher in infants and older children with GMR ranging from 1.12 to 1.20. The steady-state exposures across the age groups are generally within the range of those in adults.

Table 6-5. Anidulafungin Exposure and PK Parameters in Pediatric and Adult Patients by Age Groups (DUKE IIR study and A8851008)

	1 month to <2 years[a]	2 to <5 years	5 to <18 years	≥18 years[b]
Dose	3.0 mg/kg (LD) and 1.5 mg/kg (MD) (not to exceed 200 mg/100 mg (LD/MD)			200 mg (LD) and 100 mg (MD)
N	23	19	30	83
$AUC_{0\text{-}24,ss}$				
Mean (SD)	82.91 (43.74)	82.81 (31.9)	86.77 (31.12)	91.11 (38.93)
GM (CV%)	76.3 (39.1)	77.3 (39.8)	81.9 (35.9)	84.1 (41.5)
Median (Range)	67.52 (49.09-260.64)	80.01 (35.8-161.65)	80.49 (28.3-197.79)	85.09 (30.8-246.9)
$C_{max,ss}$				
Mean (SD)	7.12 (2.89)	7.13 (2.8)	6.48 (1.89)	6.14 (2.87)
GM (CV%)	6.71 (34.5)	6.61 (43.1)	6.22 (30.3)	5.6 (45.2)
Median (Range)	6.55 (3.93-17.81)	6.97 (2.63-12.64)	6.21 (2.56-12.42)	5.84 (1.9-19.15)
$C_{min,ss}$				
Mean (SD)	2.46 (1.44)	2.51 (1.11)	2.52 (0.96)	2.71 (1.31)
GM (CV%)	2.22 (45.6)	2.29 (46.1)	2.35 (41)	2.46 (45)
Median (Range)	1.92 (1.17-8.12)	2.46 (1.01-5.36)	2.34 (0.62-5.9)	2.47 (0.87-9.06)

Source: Adapted from Table 1, Applicant's response (received on 5/15/2020) to Clinical Pharmacology IR (dated 4/23/2020).
[a] The patients are from DUKE IIR study (n=6) and A8851008 (n=17).
[b] The referenced adult PK data (Age >18 years) were estimated based on the two adult studies, A8851011 and A8851019.
LD (loading dose), MD (maintenance dose)

The steady-state exposures in pediatric patients enrolled in Study A8851008 are presented by age groups in Table 6-6. The mean AUC in the infant group (1 month to < 2 years) in Study A8851008 was approximately 23% lower compared to those in other pediatric age groups and adults. It is noteworthy that the between patient variability in AUC, given as the %CV, was 25% in the 1 month to <2-year-old pediatric patients and ranged from 35% to 43% in the older pediatric patients and adults. Thus, the reduction in the AUC for the youngest pediatric age group was within the variability in AUC (%CV) observed for all the other age groups. In addition, the range of AUC estimates in the 1 month to <2-year-old age group was within the range of AUC estimates shown in Tables 6-5 and 6-6 for the older pediatric patients and adults. No E-R relationship has been established for ICC indication in adult patients. Therefore, exploratory E-R analyses were performed by the Pharmacometrics reviewer based on the pediatric patients (n=62) from Study A8851008 (Refer to Section 17.3 for the detailed E-R analyses). In graphical examinations (Figure 6-1) of the relationships between the exposure metrics ($AUC_{0\text{-}24,ss}$, and $AUC_{0\text{-}24,ss}$ /MIC) and the global response rate at EOVIT or EOT, no apparent trend of loss of efficacy was observed at the lower exposures in the 1 month to <2 year old age group in

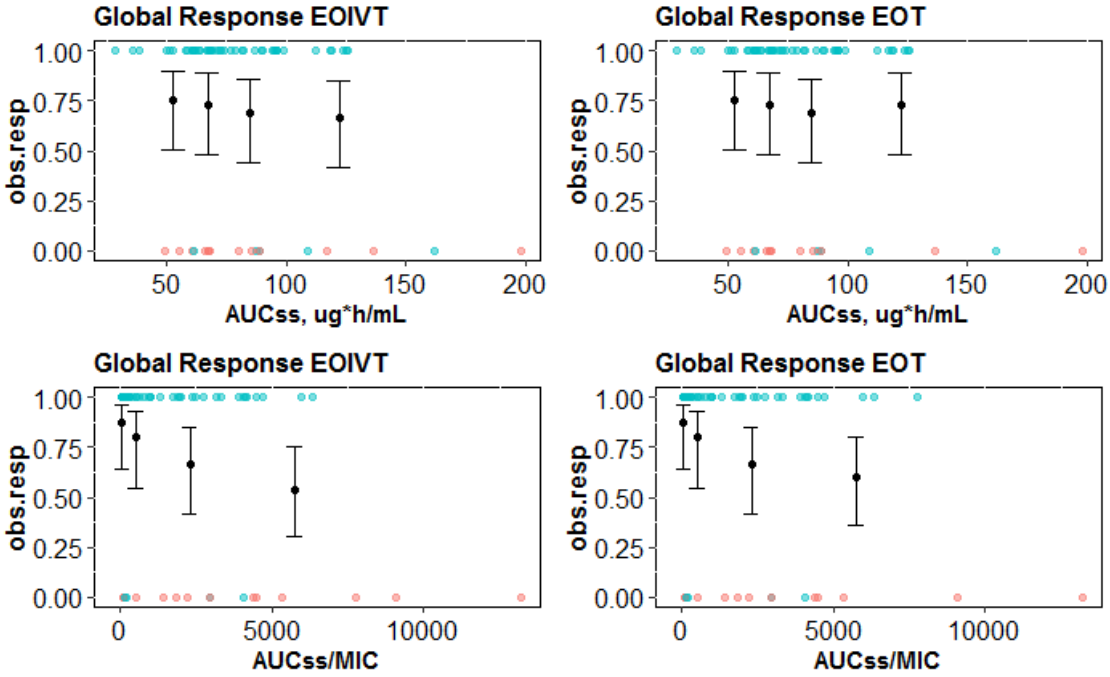
A8851008. Furthermore, the global responses at EOIVT by age groups were similar across the age groups in Study A8851008 (Refer to Section 7, Clinical Efficacy).

Table 6-6. Anidulafungin Exposure and PK Parameters in Pediatric and Adult Patients by Age Groups (A8851008)

	1 month to <2 years	2 to <5 years	5 to <18 years	≥18 years [a]
Dose	**3.0 mg/kg (LD) and 1.5 mg/kg (MD)**			**200 mg (LD) and 100 mg (MD)**
N	17	19	30	83
$AUC_{0\text{-}24,ss}$ (µg*h/mL)				
Mean (SD)	69.87 (17.65)	82.81 (31.9)	86.77 (31.12)	91.11 (38.93)
GM (CV%)	68 (24.2)	77.3 (39.8)	81.9 (35.9)	84.1 (41.5)
Median (Range)	66.42 (49.09-112.09)	80.01 (35.8-161.65)	80.49 (28.3-197.79)	85.09 (30.8-246.9)
$C_{max,ss}$ (µg/mL)				
Mean (SD)	6.69 (1.86)	7.13 (2.8)	6.48 (1.89)	6.14 (2.87)
GM (CV%)	6.46 (27.5)	6.61 (43.1)	6.22 (30.3)	5.6 (45.2)
Median (Range)	6.33 (4.34-10.18)	6.97 (2.63-12.64)	6.21 (2.56-12.42)	5.84 (1.9-19.15)
$C_{min,ss}$ (µg/mL)				
Mean (SD)	1.98 (0.58)	2.51 (1.11)	2.52 (0.96)	2.71 (1.31)
GM (CV%)	1.91 (28.7)	2.29 (46.1)	2.35 (41)	2.46 (45)
Median (Range)	1.85 (1.17-3.27)	2.46 (1.01-5.36)	2.34 (0.62-5.9)	2.47 (0.87-9.06)

Source: Adapted from Table 2, Applicant's response (received on 5/15/2020) to Clinical Pharmacology IR (dated 4/23/2020).
[a] The referenced adult PK data (Age >18 years) were estimated based on the two adult studies, A8851011 and A8851019.

Figure 6-1. E-R relationships in Pediatric Patients for ICC (A8851008)



Source: Reviewer's analysis. Blue dots represent the individual response data (1=success, and 0=failure). "Indeterminate" data were treated as "failure". Red dots represent the individual data which was coded as indeterminate. Black dots represent the mean response rate for each quartile of the corresponding exposure metric ($AUC_{0\text{-}24,ss}$, and $AUC_{0\text{-}24,ss}$ /MIC). Error bars represent the 95% confidence intervals for each mean estimate.

The referenced AUC estimates for the adult age group >18 years in Table 6-5 and Table 6-6 are in general lower compared to those presented in the current approved labeling. The AUC values used in Tables 6-5 and 6-6 were estimated based on adult patients with ICC (or at high risk of ICC) from two studies, A8851011 and A8851019, which have not been previously reviewed by FDA. The Applicant noted that the PK variability and population characteristics (body weight and disease status) potentially explain these differences (see Table 6-7). The review team determined that the adult PK values based on these two studies are acceptable to be used as the reference to assess the exposure in pediatric patients with ICC because: 1) the PK samples from these adult studies were analyzed with the same bioanalytical methods as the pediatric PK samples 2) the population PK model describes the adult PK data reasonably well, and 3) the adult patients for these studies had the intended indication (ICC) and received the approved adult dose for ICC.

Table 6-7. Comparison of PK parameters between Current Submission and Approved Labeling

PK Parameter	Current submission	Approved Labeling (as of 7/29/2020)	
	200 mg (LD)/ 100 mg (MD)	**200 mg (LD)/ 100 mg (MD)**	**100 mg (LD)/ 50 mg (MD)**
Mean $AUC_{0\text{-}24,ss}$ (CV%), µg*h/mL	91.1 (42.7)	110.3 (32.5)	55.2 (32.5)
Mean $C_{min,ss}$ (CV%), µg/mL	2.71 (48.3)	3.3 (41.8)	1.6 (42.1)
Patient Demographics	83 ICC patients (or at high risk of ICC) from A8851011 and A8851019	262 patients from two studies for esophageal candidiasis [(EC), VER002-4 and VER002-11]; one study for ICC (VER002-6); one study for invasive aspergillosis [(IA), VER002-7]	
Mean Body Weight (Range), kg	A8851011 (n=33): 77.2 (37.8-122.1) kg A8851019 (n=50): 70 (48-240) kg	Pooled studies (n=262): 61 (31-154) kg	
Source: Reviewer's table based on Applicant's response (received on 5/15/2020) to Clinical Pharmacology IR (dated 4/23/2020)			

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7-1 NDA 21-632: Listing of Clinical Trials

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Uncontrolled Studies to Support Efficacy and Safety						
A8851008	NCT00761267	Open-label, non-comparative, PK, safety and efficacy of anidulafungin in patients with invasive candidiasis including candidemia *Note: It was initiated in Feb. 2009 and completed (i.e., last subject/ last visit) in Feb. 2018.*	Anidulafungin IV: 3mg/kg loading dose x 1 followed by 1.5mg/kg per day *Note: Option to switch to oral fluconazole after 10 days of anidulafungin treatment*	Primary: Safety and tolerability of anidulafungin when used to treat children with invasive candidiasis and/or candidemia. Secondary: All efficacy evaluations. Efficacy was assessed by global response at EOIVT, EOT, and the 2- and 6-week follow-up visits.	At least 10 days up to a max. of 35 days / follow-up 6 weeks	72 pediatric patients 68 of 72 patients received anidulafungin	Pediatric patients 1 month to < 18 years of age in 3 cohorts: 1 month to 2 years: n=19. 2 to < 5 years: n=19. 5 to < 18 years: n=30.	26 sites in 10 countries *Note: An additional 47 sites were supplied study drug but did not enroll*
		Other studies pertinent to the review of efficacy or safety						
Duke IIR (VER001)	NCT00734500	Open-label, single center, pharmacokinetic study of anidulafungin neonates and infants	Anidulafungin IV: 3mg/kg loading dose x 1 followed by 1.5mg/kg per day	PK, Safety and tolerability	1 to 5 days	15 pediatric patients	Neonates and infants < 24 months of age	1 site in one center in USA

7.2. Review Strategy

The sources of data used in the evaluation of efficacy and safety of Anidulafungin for Injection included study reports, data sets [raw data, Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references which can be found at the following link: \\CDSESUB1\evsprod\NDA021632\0091

Patient-level data from Study A8851008 were used to evaluate the efficacy of IV anidulafungin for the treatment of invasive candidiasis in pediatric patients. Efficacy was a secondary outcome in this study. Given the comparable exposures of anidulafungin in pediatric patients to adult patients with candidemia and other forms of invasive candidiasis, efficacy is primarily extrapolated from the adult data in the phase 3 clinical trial, VER002-9. VER002-9 was the registrational trial for the approval of anidulafungin for treatment of invasive candidiasis/candidemia in adults.

The primary source of patient-level safety data was adverse events reported during inpatient hospitalization and 6-week follow up period in pediatric subjects enrolled in study A8851008. Potential adverse drug reactions were identified by evaluation of adverse events during anidulafungin treatment and in the post treatment period and by comparisons to adverse reactions reported for adults in study VER002-9 and the known safety profile of echinocandin antifungals. Additional supportive safety data were from two small PK/ safety study in neonates and infants, postmarket safety data from the applicant's global safety database for anidulafungin, and published literature. The Applicant's literature review was used to identify additional adverse reactions reported in other clinical studies and in the post-market setting. The reviewers' assessments of the data are presented in this review.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study A8851008

Trial Design

Study A8851008 was an open-label, non-comparative, multicenter study designed to assess the safety, efficacy, and PK of anidulafungin for the treatment of invasive candidiasis including candidemia in pediatric patients 1 month to < 18 years of age. The study was a multinational study conducted in 10 countries which enrolled subjects: Brazil, Canada, Greece, Italy, Republic of Korea, Russia, Spain, Taiwan, United Kingdom, and the United States. Enrollment was stratified by age (1 month to < 2 years, 2 to < 5 years, and 5 to < 18 years).

Eligible subjects included males or females aged 1 month to < 18 years of age with a definitive diagnosis of invasive candidiasis/candidemia or only for subjects 1 month to < 2 years who were at high risk for candidiasis. A definitive diagnosis of invasive candidiasis/candidemia was based on the growth of *Candida* spp. from a blood and/or tissue culture obtained from a normally sterile site and at least 1 clinical criterion at the time of study entry or within 96 hours prior to study entry. Clinical criteria included fever, hypothermia, hypotension, and other signs or symptoms of invasive candidiasis/candidemia such as feeding intolerance, bloody stools, abdominal distension, thrombocytopenia, lethargy, color change, hyperglycemia, glycosuria, or unexplained metabolic acidosis. The culture results to confirm *Candida* species may have been pending at the time of enrollment as long as there was mycologic evidence highly suggestive of *Candida* spp. (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 (e.g., blood and/or tissue). Subjects were not eligible if they were premature neonates born at gestation of less than 36 weeks, failed antifungal treatment with any systemic echinocandin for the episode of candidiasis/candidemia, required continued treatment with another systemic antifungal agent, had a life expectancy < 72 hours, or had suspected *Candida* meningitis. Additionally, subjects were not to have received more than 48 hours of systemic antifungal therapy for the enrolling *Candida* infection. However, prior antifungal prophylaxis was allowed.

All subjects received anidulafungin IV treatment [3.0 mg/kg loading dose on Day 1 (not to exceed 200 mg) followed by 1.5 mg/kg (not to exceed 100 mg) maintenance dose daily thereafter]. Treatment with anidulafungin was to be administered for a minimum of 10 days to a maximum of 35 days. After at least 10 days of IV treatment (5 days for those enrolled under Amendment 9 without microbiologically-confirmed *Candida* infection), there was an option to switch to oral fluconazole (6 to 12 mg/kg/day, maximum 800 mg/day) provided the subject met prespecified criteria. All of the following criteria had to be met: afebrile for at least 24 hours; able to tolerate oral medication; documentation of 2 blood cultures negative for *Candida* spp.

separated by at least 24 hours; *Candida* spp. from any other site of infection, if identified at enrollment, was eradicated or presumed eradicated; the specific *Candida* isolate identified at study entry was susceptible (or presumed susceptible) to fluconazole; and signs and symptoms of *Candida* infection were improved such that the investigator considered it was appropriate to switch to oral fluconazole.

Study treatment was to continue for a minimum of 14 days from the time of the last negative culture (defined as the second of 2 consecutive negative cultures separated by at least 24 hours following the last positive culture) and with improvement of clinical signs and symptoms of candidemia or invasive candidiasis. The last day of anidulafungin IV treatment was considered the end of IV treatment (EOIVT). The last day of all treatment was considered the end of treatment (EOT). Subjects were to be followed for a total of 6 weeks after EOT and return for 2-week and 6-week follow-up visits.

The doses of anidulafungin used in the study were expected to achieve total exposures comparable to those observed in the Phase 3 study of subjects aged 16 years and older with invasive candidiasis/candidemia where anidulafungin was compared to fluconazole. PK studies demonstrated that pediatric body weight was the primary consideration in achieving anidulafungin plasma concentrations comparable to adults and that pediatric subjects receiving 1.5 mg/kg/day IV anidulafungin had concentration profiles and drug exposures similar to those in adults receiving 100 mg/day.

An external Data Monitoring Committee (E-DMC) was responsible for ongoing monitoring of the safety of subjects during the conduct of the trial. The first E-DMC meeting was conducted after at least 8 subjects were enrolled; thereafter, meetings were conducted every 6 months unless no subjects were enrolled or there were no new significant changes in safety and/or efficacy data that were previously reported. Over the course of the study, the only recommendation from the E-DMC was to continue the study without modification.

Study Endpoints

The primary objective of the study was to assess the safety and tolerability of anidulafungin when used to treat children with invasive candidiasis and/or candidemia. Therefore, all efficacy evaluations were considered secondary endpoints.

Efficacy was assessed primarily by global response at EOIVT, EOT, and the 2- and 6-week follow-up visits. Global response was derived programmatically based on the investigator's assessment of clinical and microbiological response. A successful global response required both a clinical response of success (cure or improvement) and microbiological response of success (eradication or presumed eradication). Global response was categorized as a failure if there was a clinical response of failure and/or a microbiological response of failure (persistence or new infection at follow-up or relapse of infection at follow-up). Global response was categorized as indeterminate if either clinical or microbiological response were indeterminate

and neither response was a failure. A global response of failure at any visit was carried forward to all subsequent visits. Additionally, if a subject received concomitant antifungal medications for 2 or more days after the start of study medication until EOT for any reason, global response was imputed as a failure for all visits that occurred after the antifungal medication was taken.

Additional efficacy endpoints included: relapse (recurrence) at the 2- and 6-week follow-up visits, new infection at the 2- and 6-week follow-up visits, and all-cause-mortality.

Safety was evaluated through assessment of adverse events and monitoring of clinical laboratory tests (hematology and serum chemistry), temperature, and physical examination results.

Statistical Analysis Plan

The statistical analysis plan (SAP) was finalized as Version 6 dated October 6, 2016 and implemented prior to database lock. Most changes were minor to bring the SAP in agreement with changes made in the protocol amendments. Additional changes included clarifying the definition of the global response endpoint and analysis as well as the addition of the interim analysis.

Analysis Populations

The safety population consists of all enrolled subjects who received at least one dose of study medication. The safety population is used for all safety analyses.

The modified intent-to-treat (MITT) population includes all subjects who received at least one dose of study drug and who have a confirmed *Candida* infection. The primary efficacy analysis population is the MITT population.

The per-protocol (PP) analysis set consists of a subset of the MITT population who completed a minimum of 10 days of treatment with IV anidulafungin, unless declared a clinical and/or microbiologic failure; received total antifungal treatment (IV only, IV + Oral) for a minimum duration of 14 days, unless declared a clinical and/or microbiologic failure; did not receive more than 48 hours of systemic antifungal therapy (for treatment of current *Candida* infection) prior to first dose of study drug; did not have a prosthetic device and/or vascular catheter (including central venous catheter or an implantable port) at a suspected site of infection unless the device was removed at study entry or soon after first dose of study drug; did not take more than 1 day of protocol prohibited antifungal therapy concomitant with study therapy, unless declared a clinical and or microbiologic failure; reached the 6 weeks Follow up visit unless the subject died or withdrew consent prior to 6 week follow up; and did not have a protocol violation that could have an impact on the efficacy endpoints. Additional supportive efficacy analyses were conducted by the Applicant with the PP analysis set. However, this review will focus on the MITT population.

Analysis Methods

No hypothesis testing was conducted. The efficacy results of the study are summarized descriptively overall and by age group. Response rates and 95% exact confidence intervals for the proportions were calculated. For the global response, missing values were treated as failures.

Sample Size Calculation

The sample size chosen for the study was not based on statistical considerations. A sample size of 60 evaluable subjects was chosen based on the number of subjects estimated to be necessary to provide adequate information for assessing efficacy, safety, and tolerability in children.

Interim Analysis

Protocol Amendment 9 allowed for the conduct of an interim analysis of the safety, PK, and efficacy data of the 2 to < 5 years and 5 to <18 years cohorts when the target enrolment of 20 ± 2 subjects was achieved and had completed the study. Enrolment in the 1 month to < 2 years cohort continued until target enrollment was achieved. This was considered an interim analysis since the overall study was ongoing in the youngest cohort.

Protocol Amendments

The original protocol was dated December 7, 2001. There were 9 amendments to the protocol with the first 2 amendments made prior to enrolling any subjects. Most changes to the protocol were for clarification purposes. Changes that impacted aspects of study design included the following:

- Protocol Amendment 3 (September 21, 2009) changed the criteria for confirmation of invasive candidiasis/candidemia (based on the growth of *Candida* spp. from a culture obtained from a normally sterile site within 96 hours prior to enrollment) to also allow mycological evidence highly suggestive of *Candida* spp. (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) as long as culture confirmation of *Candida* spp. was obtained within 96 hours post treatment initiation.
- Protocol Amendment 4 (August 19, 2010) amended exclusion criteria to allow for the enrollment of subjects with *Candida* endocarditis or *Candida* osteomyelitis.
- Protocol Amendment 9 (September 16, 2016) broadened the study population to include children aged 1 month to < 2 years who were at high risk for candidiasis in order to accelerate the availability of PK and safety data in this lowest age group as recommended by the EMA. Additionally, key exclusion criteria were amended, including the removal of exclusion criteria limiting prior systemic antifungal therapy use to no more than 48 hours and revised text for the removal of prosthetic devices and/or

vascular catheters at the suspected site of infection. The interim analysis of the 2 to < 5 years and 5 to <18 years cohorts was added.

Most subjects were enrolled prior to the date of Protocol Amendment 9 including all subjects in the 5 to < 18 years cohort, all but 1 subject in the 2 to < 5 years cohort, and 11 of 20 subjects in the 1 month to < 2 years cohort. It should be noted that although Protocol Amendment 9 removed the exclusion criterion that limited prior systemic antifungal therapy use to no more than 48 hours, no subjects enrolled under Protocol Amendment 9 received more than 48 hours of prior systemic antifungal therapy for the enrolling *Candida* infection. The modifications to the protocol did not have an impact on the integrity of the trial or the interpretation of the results.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that "This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants."

Data Quality and Integrity

In general, the data submitted by the Applicant were acceptable and there were no issues noted with regard to the data quality and integrity.

Financial Disclosure

The Applicant provided a list of the trial investigators and any stated conflict of interest. Nine investigators had disclosable financial interest or arrangements, see section 17.2.

Patient Disposition

A total of 70 subjects were enrolled in the study. Two subjects (enrolled prior to Amendment 9) did not receive study medication because the permitted window for prior antifungal therapy had elapsed before study treatment could start. Therefore, the Safety population consisted of 68 subjects. Four additional subjects were excluded from the MITT population. Two subjects were excluded from the MITT population because the results of their screening cultures did not show growth of *Candida* spp. The other 2 subjects excluded from the MITT population were enrolled under Protocol Amendment 9 as being at high risk for candidiasis and did not have microbiologically-confirmed *Candida* infection.

Table 8-1: Analysis Populations

Analysis Population	Age Group			Overall
	1 Month to < 2 years	2 to < 5 years	5 to < 18 years	
	N (%)	N (%)	N (%)	N (%)
Enrolled	20 (100)	20 (100)	30 (100)	70 (100)
Safety	19 (95)	19 (95)	30 (100)	68 (97)
MITT	16 (80)	18 (90)	30 (100)	64 (91)
PP	10 (50)	11 (55)	19 (63)	40 (57)

Overall, 69% of enrolled subjects completed treatment and 31% discontinued treatment. The reasons for discontinuing treatment are presented in Table 8-2. Of the 7 subjects who discontinued treatment due to an adverse event, 6 subjects discontinued while receiving anidulafungin and 1 subject discontinued while receiving oral fluconazole. The 2 subjects who discontinued treatment due to a protocol violation both required further treatment with IV fluconazole which was not allowed by the protocol. The 2 subjects who discontinued treatment due to not meeting entry criteria were discontinued from treatment after the final microbiology report showed no growth of *Candida* spp. The subject who discontinued due to other reason required 5 weeks of antifungal treatment due to hepatic lesions but IV anidulafungin could not be administered at home and the subject could not tolerate or absorb oral antifungals.

The majority (83%) of subjects completed the study through the 6-week follow-up visit. Twelve subjects prematurely discontinued the study, including the 2 subjects who did not receive treatment. The most common reason for premature discontinuation from the study was due to death of the subject (n=8).

Table 8-2: Subject Disposition

	Age Group			Overall
	1 Month to < 2 years	2 to < 5 years	5 to < 18 years	
	N (%)	N (%)	N (%)	N (%)
Enrolled	20 (100)	20 (100)	30 (100)	70 (100)
Completed Treatment	13 (65)	13 (65)	22 (73)	48 (69)
Discontinued Treatment	7 (35)	7 (35)	8 (27)	22 (31)
Adverse event	2 (10)	2 (10)	3 (10)	7 (10)
Death	0	1 (5)	2 (7)	3 (4)
Insufficient clinical response	0	0	1 (3)	1 (1)
Insufficient microbiological response	2 (10)	0	1 (3)	3 (4)
Protocol violation	0	1 (5)	1 (3)	2 (3)
Withdrew consent	0	1 (5)	0	1 (1)
Did not meet entry criteria	1 (5)	1 (5)	0	1 (1)
No treatment received	1 (5)	1 (5)	0	2 (3)
Other	1 (5)	0	0	1 (1)
Completed Study	18 (90)	16 (80)	24 (80)	58 (83)
Discontinued Study	2 (10)	4 (20)	6 (20)	12 (17)
Death	1 (5)	2 (10)	5 (17)	8 (11)
Lost to follow-up	0	0	1 (3)	1 (1)
Withdrew consent	0	1 (5)	0	1 (1)

	Age Group			
	1 Month to < 2 years	2 to < 5 years	5 to < 18 years	Overall
	N (%)	N (%)	N (%)	N (%)
No treatment received	1 (5)	1 (5)	0	2 (3)

Source: Reviewer conducted analysis using ADSL dataset

Protocol Violations/Deviations

Potentially important protocol deviations reported for all enrolled subjects are summarized in Table 8-3. The most commonly reported potentially important deviations were in the investigational product category (59 subjects, 84.3%). Within the investigational product category, the primary reasons were infusion rate not being within the specified range for 20 subjects (in most cases the infusion rate exceeded the protocol specified rate of 1.1 mg/min) and overfill volume not removed from IV bag for all doses of anidulafungin administered for 31 subjects. The Applicant noted that only 1 treatment-related adverse event was reported in relation to the infusion rate exceeding the protocol specified rate. The Applicant conducted a detailed assessment of the potential impacts of the failure to remove overfill volume. They concluded that the failure to remove overfill volume could have resulted in a final drug concentration less than the target leading to a potential under-dosing (1 to 9% lower dose) of anidulafungin. However, given the known variability in anidulafungin exposure in adults and pediatric patients, this potential difference in dose would not be of a magnitude considered to be clinically impactful. Therefore, the reported protocol deviations are not expected to have had an impact on safety or efficacy analyses and the overall study results.

Table 8-3: Protocol Deviations- Enrolled Subjects

Category	Age Group			Overall
	1 Month to < 2 years (N=20) n (%)	2 to < 5 years (N=20) n (%)	5 to < 18 years (N=30) n (%)	(N=70) n (%)
Concomitant Medications	0	1 (5.0)	3 (10.0)	4 (5.7)
Inclusion/Exclusion Criteria	4 (20.0)	4 (20.0)	4 (13.3)	12 (17.1)
Informed Consent	1 (5.0)	2 (10.0)	4 (13.3)	7 (10.0)
Investigational Product	15 (75.0)	15 (75.0)	29 (96.7)	59 (84.3)
Laboratory	11 (55.0)	12 (60.0)	21 (70.0)	44 (62.9)
Procedures/Tests	7 (35.0)	8 (40.0)	11 (36.7)	26 (37.1)
Protocol Specific Discontinuation Criteria	1 (5.0)	0	1 (3.3)	2 (2.8)
Randomization/Stratification	1 (5.0)	2 (10.0)	3 (10.0)	6 (8.6)
Safety Reporting	2 (10.0)	2 (10.0)	1 (3.3)	5 (7.1)
Visit Schedule	7 (35.0)	3 (15.0)	7 (23.3)	17 (24.3)

Source: Reviewer conducted analysis using DV and SUPPDV datasets

Demographic and Other Baseline Characteristics

Table 8-4 summarizes demographic and baseline characters of subjects in the Safety population. More subjects (n=30) were in the 5 to < 18 years age group compared with the

1 month to < 2 years and 2 to < 5 years age groups which both had 19 subjects. Overall, there were more males than females, and this was consistent across age groups. The majority of the subjects were white (79.4%). Approximately 26% of the subjects were from the United States. The mean baseline weight was 22.6 kg.

Table 8-4: Demographic Characteristics (Safety Population)

Parameter	Age Group			Overall
	1 Month to < 2 years (N=19)	2 to < 5 years (N=19)	5 to < 18 years (N=30)	(N=68)
Sex				
Male	10 (52.6)	11 (57.9)	17 (56.7)	38 (55.9)
Female	9 (47.4)	8 (42.1)	13 (43.3)	30 (44.1)
Race				
White	19 (100)	15 (78.9)	20 (66.7)	54 (79.4)
Black	0	1 (5.3)	0	1 (1.5)
Asian	0	2 (10.5)	4 (13.3)	6 (8.8)
Other	0	1 (5.3)	6 (20.0)	7 (10.3)
Age (years)				
Mean (sd)	0.9 (0.5)	3.1 (0.7)	10.7 (3.7)	5.8 (5.0)
Median	0.9	3	10	4
Min, Max	0.1, 1.8	2.3, 4	5, 17	0.1, 17
Country				
United States	5 (26.3)	7 (36.8)	6 (20.0)	18 (26.5)
Other	14 (73.7)	12 (63.2)	24 (80.0)	50 (73.5)
Weight (kg)				
Mean (sd)	7.9 (3.0)	14.6 (2.9)	36.9 (20.6)	22.6 (19.0)
Median	7.9	14.5	30	16
Min, Max	2.3, 13	10.0, 19.3	13.4, 85.7	2.3, 85.7

Source: Reviewer's analysis using ADSL dataset

The site of infection in the majority of the subjects was blood only (92.2%). Two subjects had candidemia as well as an infection at another sterile site. This included a subject aged 1 month to < 2 years who had candidemia, urinary tract infection and *Candida*-positive stool (colonization); and a subject aged 2 to < 5 years who had candidemia and infection in the eye and urinary tract. Three subjects had infection at a sterile site (other than blood) only; all were abdominal (abscess and peritonitis). Overall, the most common baseline pathogens isolated were *C. albicans* (39.1%), *C. parapsilosis* (26.6%), and *C. tropicalis* (14.1%). Among the subjects in the 1 month to < 2 years and 2 to < 5 years age groups, *C. albicans* was the most common baseline pathogen isolated, while *C. parapsilosis* was the most common baseline pathogen isolated in the 5 to < 18 years age group. Two subjects, both in the 2 to < 5 years age group, had multiple baseline *Candida* species isolated. One subject had *C. glabrata* and *C. famata* isolated in the blood. The other subject had *C. albicans* isolated in the urine and *C. guilliermondii* isolated in the blood.

Table 8-5: Primary Diagnosis of Infection by Site of Infection and Baseline *Candida* species (MITT Population)

Parameter	Age Group			Overall
	1 Month to < 2 years (N=16)	2 to < 5 years (N=18)	5 to < 18 years (N=30)	(N=64)
Site of Infection				
Blood only	14 (87.5)	16 (88.9)	29 (96.7)	59 (92.2)
Blood and Other Sterile Site	1 (6.3)	1 (5.6)	0	2 (3.1)
Sterile Site (other than blood) only	1 (6.3)	1 (5.6)	1 (3.3)	3 (4.7)
Baseline *Candida* Species*				
C. albicans	7 (43.8)	10 (55.6)	8 (26.7)	25 (39.1)
C. parapsilosis	5 (31.3)	2 (11.1)	10 (33.3)	17 (26.6)
C. tropicalis	2 (12.5)	1 (5.6)	6 (20.0)	9 (14.1)
C. lusitaniae	0	1 (5.6)	4 (13.3)	5 (7.8)
C. glabrata	1 (6.3)	2 (11.1)	1 (3.3)	4 (6.3)
C. guilliermondii	0	2 (11.1)	1 (3.3)	3 (4.7)
C. famata	0	1 (5.6)	0	1 (1.6)
C. haemulonii	0	1 (5.6)	0	1 (1.6)
Candida spp. unidentified	1 (6.3)	0	0	1 (1.6)

Source: Adapted from Tables 14.2.4 and 14.2.3 of Protocol A8851008 Study Report
*As identified by the local microbiology laboratory. Subjects could have multiple *Candida* species at baseline. The reference microbiology laboratory identified the *C. haemulonii* isolate as *Kodamaea ohmeri* and the unspecified *Candida* species isolate as *Candida parapsilosis.*

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Since subjects were hospitalized for IV administration of anidulafungin, compliance with study treatment was high. All subjects treated with anidulafungin had an overall compliance rate of ≥ 90%.

Overall, 68 subjects received treatment with anidulafungin for a median duration of 11 days. A total of 31 subjects were switched to oral treatment with fluconazole. The median duration of treatment with fluconazole for these subjects was 8 days. The median total duration of overall antifungal treatment (anidulafungin + fluconazole) was 17 days. A summary of treatment duration by age group and overall for the Safety population is presented in Table 8-6.

Table 8-6: Treatment Duration (Safety Population)

Treatment	Age Group			Overall
	1 Month to < 2 years	2 to < 5 years	5 to < 18 years	
Anidulafungin (IV)	(n=19)	(n=19)	(n=30)	(n=68)
Median duration (days)	13.0	11.0	11.0	11.0
Range	4-30	1-28	1-35	1-35
Oral fluconazole (optional switch)	(n=6)	(n=10)	(n=15)	(n=31)
Median duration (days)	9.5	9.0	7.0	8.0
Range	3-15	4-16	1-52	1-52
Total (anidulafungin + fluconazole**)**	(n=19)	(n=19)	(n=30)	(n=68)
Median duration (days)	16.0	18.0	17.5	17.0
Range	4-38	1-37	1-62	1-62

Source: Adapted from Table 21 of Protocol A8851008 Study Report

All subjects in the Safety population used at least 1 concomitant medication. During the treatment period, the 3 most commonly used concomitant medications were paracetamol (n=29, 42.6%), vancomycin (n=25, 36.8%), and furosemide (n=23, 33.8%). Overall, 19 (27.9%) subjects received antifungal drug treatment between EOT and the 6-week follow-up visit. This included 8 (42.1%) subjects aged 1 month to < 2 years, 5 (26.3%) subjects aged 2 to < 5 years, and 6 (20.0%) subjects aged 5 to < 18 years. The most commonly used antifungal treatment was fluconazole, which was used as prophylaxis (allowed per protocol) in 11 of the 19 subjects. Subjects who received antifungal drug treatment that was not used as prophylaxis after EOT were considered clinical failures from the point of receipt of concomitant antifungal treatment.

Efficacy Results – Primary Endpoint

Table 8-7 summarizes global response at EOIVT, EOT, the 2-week follow-up, and the 6 week-follow-up for the MITT population overall and by age group. Overall, a successful global response was observed in 70.3% (45/64) subjects at EOIVT. Considering the small number of subjects, there are no notable trends observed with respect to global response by age group. Except for a single subject aged 5 to < 18 years, the results at EOT were the same as EOIVT. This subject was assessed as having a successful global response at EOT (and both follow-up visits) but indeterminate at EOIVT because although clinical improvement was noted at EOIVT, the microbiological response was indeterminate since a follow-up culture of the liver abscess was not performed. Follow-up blood cultures were performed in this subject, and they remained negative.

Most (4 subjects) of the global response failures at EOIVT were due to microbiological persistence. Although a subject aged 2 to < 5 years was assessed as having clinical improvement and microbiological eradication at the end of anidulafungin treatment, this subject was considered a global response failure because treatment was continued with IV fluconazole due to *Candida* in the urine. One subject aged 5 to < 18 years was a global response failure at EOIVT due to clinical failure even though there was microbiological eradication.

Global response was assessed as indeterminate for approximately 20% of subjects in the MITT population. Most were assessed as indeterminate at EOIVT because they discontinued treatment due an adverse event and/or received an alternative antifungal (6 subjects) or the subject died while on treatment (4 subjects). The other subjects assessed as indeterminate at EOIVT include 1) the subject discussed above who was a global success at EOT and all follow-up visits; 2) a subject who was clinically improved but did not have a microbiological assessment at EOIVT, discontinued oral fluconazole due to an adverse event, and then died; and 3) a subject who was eradicated but had an indeterminate clinical response at EOIVT/EOT and was a clinical failure with recurrence at the 6-week follow-up. At the follow-up timepoints, the missing category includes subjects who died and 1 subject who withdrew from the study after being declared a global success at EOIVT/EOT. Although the rate of indeterminate appears high,

these subjects should more likely be considered failures with the exception of the subject who was a global success at EOT and all follow-up visits. Therefore, the rates of successful global response are not expected to be underestimates given the high rate of subjects classified as indeterminate.

Table 8-7: Global Response (MITT population)

	Age Group			
Time Point	**1 Month to < 2 years**	**2 to < 5 years**	**5 to < 18 years**	**Overall**
Global Response	(n=16)	(n=18)	(n=30)	(n=64)
EOIVT				
Success	11 (68.8)	14 (77.8)	20 (66.7)	45 (70.3)
Exact 95% CI	(41.3, 89.0)	(52.4, 93.6)	(47.2, 82.7)	(57.6, 81.1)
Failure	2 (12.5)	1 (5.6)	3 (10.0)	6 (9.4)
Indeterminate	3 (18.8)	3 (16.7)	7 (23.3)	13 (20.3)
EOT				
Success	11 (68.8)	14 (77.8)	21 (70.0)	46 (71.9)
Exact 95% CI	(41.3, 89.0)	(52.4, 93.6)	(50.6, 85.3)	(59.2, 82.4)
Failure	2 (12.5)	1 (5.6)	3 (10.0)	6 (9.4)
Indeterminate	3 (18.8)	3 (16.7)	6 (20.0)	12 (18.8)
2-week Follow-up				
Success	11 (68.8)	13 (72.2)	22 (73.3)	46 (71.9)
Exact 95% CI	(41.3, 89.0)	(46.5, 90.3)	(54.1, 87.7)	(59.2, 82.4)
Failure	2 (12.5)	1 (5.6)	4 (13.3)	7 (10.9)
Indeterminate	3 (18.8)	1 (5.6)	0	4 (6.3)
Missing	0	3 (16.7)	4 (13.3)	7 (10.9)
6-week Follow-up				
Success	11 (68.8)	12 (66.7)	20 (66.7)	43 (67.2)
Exact 95% CI	(41.3, 89.0)	(41.0, 86.7)	(47.2, 82.7)	(54.3, 78.4)
Failure	2 (12.5)	2 (11.1)	6 (20.0)	10 (15.6)
Indeterminate	3 (18.8)	2 (11.1)	0	5 (7.8)
Missing	0	2 (11.1)	4 (13.3)	6 (9.4)

Source: Adapted from Table 13 of Protocol A8851008 Study Report and confirmed using ASRESP dataset

Successful global response at EOIVT by various subgroups is summarized in Table 8-8 for the MITT population. Interpretation of these results must be made with caution given the extremely limited sample sizes especially when broken down by age group.

Table 8-8: Successful Global Response at EOIVT for Various Subgroups (MITT population)

	Age Group			
	1 Month to < 2 years	**2 to < 5 years**	**5 to < 18 years**	**Overall**
	(n=16)	(n=18)	(n=30)	(n=64)
Sex				
Male	6/9 (66.7)	9/10 (90.0)	12/17 (70.5)	27/36 (75.0)
Female	5/7 (71.4)	5/8 (62.5)	8/13 (61.5)	18/28 (64.3)
Race				
White	11/16 (68.8)	13/15 (86.7)	17/20 (85.0)	41/51 (80.4)
Asian	-	1/2 (50.0)	0/4	1/6 (16.7)
Other	-	0/1	3/6 (50.0)	3/7 (42.9)

	Age Group			
	1 Month to < 2 years (n=16)	2 to < 5 years (n=18)	5 to < 18 years (n=30)	Overall (n=64)
Country				
US	1/4 (25.0)	4/6 (66.7)	5/6 (83.3)	10/16 (62.5)
Other	10/12 (83.3)	10/12 (83.3)	15/24 (62.5)	35/48 (72.9)
Site of Infection				
Blood only	9/14 (64.3)	13/16 (81.3)	20/29 (69.0)	42/59 (71.2)
Blood and Other Sterile Site	1/1	0/1	-	1/2 (50.0)
Sterile Site (other than blood) only	1/1	1/1	0/1	2/3 (66.7)

Source: Reviewer conducted analyses using ADRESP dataset

Efficacy Results – Secondary and other relevant endpoints

No subject had a relapse of infection by the 2-week follow-up visit. Three subjects (1 subject 2-to < 5 years and 2 subjects 5 to < 18 years) had a relapse after the 2-week follow-up and by the 6-week follow-up visit. No new/emergent infections were noted during the study follow-up.

Overall, the all-cause mortality rate through the 6- week follow-up was 12.5% of the MITT population. Five deaths occurred during the treatment period: 4 during the IV treatment and 1 during the oral treatment. Three deaths occurred during the follow-up period: 1 between EOT and the 2-week follow-up and 2 between the 2-week and 6- week follow-up. There is a numeric trend for increasing mortality with increasing age group. However, the small sample sizes limit any meaningful interpretation of these differences.

Table 8-9: All-cause Mortality through 6-week Follow-up (MITT Population)

Deaths	Age Group			
	1 Month to < 2 years (n=16)	2 to < 5 years (n=18)	5 to < 18 years (n=30)	Overall (n=64)
Total	1 (6.3)	2 (11.1)	5 (16.7)	8 (12.5)
Timing:				
By EOIVT	0	1 (5.6)	3 (10.0)	4 (6.3)
Between EOIVT and EOT	0	0	1 (3.3)	1 (1.6)
Between EOT and 2-week follow-up	0	0	1 (3.3)	1 (1.6)
Between 2- and 6-week follow-up	1 (6.3)	1 (5.6)	0	2 (3.1)

Source: Adapted from Table 19 of Protocol A8851008 Study Report
Note: Two additional deaths occurred after the 6-week follow-up and are not presented in the table.

8.2. Integrated Review of Effectiveness

8.2.1. Assessment of Efficacy Across Trials

There is only one trial submitted in support of the efficacy of anidulafungin in the pediatric population aged 1 month to < 18 years for the treatment of invasive candidiasis/candidemia.

8.2.2. Integrated Assessment of Effectiveness

A single non-comparative study A8851008 was conducted to provide information regarding the efficacy of anidulafungin of pediatric subjects aged 1 month to < 18 years for the treatment of invasive candidiasis/candidemia. This trial was considered acceptable since the causative pathogens, course of disease, and approach to treatment are similar in adult and pediatric patients. Therefore, achievement of comparable exposures to adult patients is expected to result in similar efficacy in pediatric patients allowing for extrapolation of efficacy in the pediatric population from the adult data.

Overall, the results observed in Study A8851008 for anidulafungin were favorable and generally consistent with those observed in the adult anidulafungin invasive candidiasis study, VER002-9, with respect to global response at all time points. The rates of successful global response for anidulafungin in Studies A8851008 and VER002-9 are presented in Table 8-10:

Table 8-10: Successful Global Response for Anidulafungin in Pediatrics and Adults (MITT Population)

Time Point	Pediatric Study A881008 (n=64)	Adult Study VER002-9 (n=127)
EOIVT	45 (70.3)	96 (75.6)
EOT	46 (71.9)	94 (74.0)
2-week follow-up	46 (71.9)	82 (64.6)
6- week follow-up	43 (67.2)	71 (55.9)

Source: Adapted from Table 8-7 of this review and Table 8 of current ERAXIS package inset

8.3. Statistical Issues

Comparative efficacy data for the pediatric population are not available as the single trial conducted was an uncontrolled study. Furthermore, the sample size of the study was small. However, evidence of efficacy in the pediatric population is primarily based on extrapolation from the adult population for this indication.

8.4. Conclusions and Recommendations

A single non-comparative study A8851008 was conducted to provide information regarding the efficacy of anidulafungin in pediatric subjects aged 1 month to < 18 years for the treatment of invasive candidiasis/candidemia. Given comparable exposures of anidulafungin for pediatric patients to adult patients, efficacy is primarily extrapolated from the adult data. Overall, the results observed in Study A8851008 for anidulafungin were favorable and generally consistent with those observed in the adult anidulafungin invasive candidiasis study, VER002-9, with respect to global response at all time points.

9 Clinical Microbiology Review

No new clinical microbiology information was included in the sNDA.

10 Review of Safety

10.1. Safety Review Approach

The sNDA contains patient level data from study A8851008 [NCT00761267], a phase 3, open-label, non-comparative, pharmacokinetic, safety and efficacy trial in pediatric patients (1 month to 17 years of age) with candidemia/invasive candidiasis.[17] The sNDA also includes a safety summary from the investigator-initiated Duke IIR research study, a phase 1, pharmacokinetic /safety study in infants and neonates[18], and a summary of postmarket safety from the Applicant's global database, and published literature.

Patients had safety assessments during hospitalization and up to six weeks post treatment. The safety population in Study A8851008 was defined as all randomized pediatric patients who received at least one dose of anidulafungin. The safety data were analyzed by subject disposition, type and frequency of adverse events, and laboratory test results. Specific adverse events, known to be associated with the echinocandin class /anidulafungin use in adults, were evaluated. Additionally, safety data from the Duke IIR study, postmarket safety reports, and published literature were reviewed.

10.2. Review of the Safety Database

Overall Exposure

The safety population included 68 patients who received at least one dose of anidulafungin. All three age cohorts, 1 month to < 2 years, 2 to < 5 years and 5 to < 18 years, received the same dose of anidulafungin: 3 mg/kg IV loading dose x 1 followed by 1.5mg/kg IV per day. The median duration of anidulafungin treatment in the safety population was 11 (1-35) days, see Table 10-1. Following treatment with anidulafungin, 31 (45.6%) patients were switched to oral fluconazole for a median of 8 (range 1-52) days. The median duration of overall treatment with anidulafungin followed by oral fluconazole was 17 (range, 1-62) days. The maximum total treatment duration (including both IV anidulafungin and oral fluconazole) was 62 days which was longer than the 49 days duration specified in the clinical protocol.

[17] Roilides E, Carlesse F, Leister-Tebbe H, et al. A Prospective, Open-label Study to Assess the Safety, Tolerability and Efficacy of Anidulafungin in the Treatment of Invasive Candidiasis in Children 2 to <18 Years of Age. Pediatr Infect Dis J 2019;38:275–279

[18] Cohen-Wolkowiez M, Benjamin DK Jr, Piper D, et al. Safety and pharmacokinetics of multiple-dose anidulafungin in infants and neonates. Clin Pharmacol Ther 2011 May;89(5):702-7.

Table 10-1 Study A8851008: Exposure to Anidulafungin - Safety Population

	Age Group			Overall
	1 Month to <2 Years	2 to <5 Years	5 to <18 Years	
Anidulafungin (IV)[a]	**(N=19)**	**(N=19)**	**(N=30)**	**(N=68)**
Duration of treatment (days), n (%)				
≤1	0	1 (5.3)	1 (3.3)	2 (2.9)
2 to 7	4 (21.1)	2 (10.5)	2 (6.7)	8 (11.8)
8 to 14	9 (47.4)	11 (57.9)	19 (63.3)	39 (57.4)
15 to 28	5 (26.3)	5 (26.3)	6 (20.0)	16 (23.5)
29 to 60	1 (5.3)	0	2 (6.7)	3 (4.4)
Median duration (days)	13.0	11.0	11.0	11.0
Range (days, minimum to maximum)	4-30	1-28	1-35	1-35
Fluconazole (oral)	**(N=6)**	**(N=10)**	**(N=15)**	**(N=31)**
Duration of treatment (days), n (%)				
≤1	0	0	1 (6.7)	1 (3.2)
2 to 7	2 (33.3)	4 (40.0)	7 (46.7)	13 (41.9)
8 to 14	3 (50.0)	5 (50.0)	4 (26.7)	12 (38.7)
15 to 28	1 (16.7)	1 (10.0)	1 (6.7)	3 (9.7)
29 to 60	0	0	2 (13.3)	2 (6.5)
Median duration (days)	9.5	9.0	7.0	8.0
Range (days, minimum to maximum)	3-15	4-16	1-52	1-52
Combined treatment: (anidulafungin + fluconazole)	**(N=19)**	**(N=19)**	**(N=30)**	**(N=68)**
Duration of treatment (days), n (%)				
≤1	0	1 (5.3)	1 (3.3)	2 (2.9)
2 to 7	4 (21.1)	2 (10.5)	2 (6.7)	8 (11.8)
8 to 14	5 (26.3)	4 (21.1)	5 (16.7)	14 (20.6)
15 to 28	7 (36.8)	11 (57.9)	17 (56.7)	35 (51.5)
29 to 60	3 (15.8)	1 (5.3)	4 (13.3)	8 (11.8)
≥61	0	0	1 (3.3)	1 (1.5)
Median duration (days)	16.0	18.0	17.5	17.0
Range (days, minimum to maximum)	4-38	1-37	1-62	1-62

Source: Module 5.3.5.2 CSR A8851008 Table 21.
Duration was defined as the total number of dosing days from first to, and including, last day of each study treatment.
Abbreviations: IV=intravenous; N=number of subjects in the population; n=number of subjects analyzed.
a. The treatment with IV anidulafungin was as per protocol; the switch to oral fluconazole was optional.

Adequacy of the Safety Database

The size of the safety database in study A8851008 was deemed adequate, although relatively small (N=68 patients), to assess the safety of anidulafungin in pediatric patients1 month to <18 years of age. Postmarket safety information for anidulafungin since its approval in adults with invasive candidiasis in 2006 and additional safety data from two small pediatric PK/safety studies were supportive of the safety of anidulafungin in pediatric patients.

10.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There were no concerns related to data integrity or quality of the submitted clinical data.

Categorization of Adverse Events

Definitions for adverse events (AEs) and serious adverse events (SAEs) in the clinical protocol were standard regulatory definitions. Laboratory abnormalities were categorized as AEs only if they were associated with signs or symptoms that required medical intervention, change in dosing or were considered a treatment emergent AE (TEAE) by the investigator. Worsening of candidemia/invasive candidiasis due to failure of study treatment was not categorized as an AE. Assessments of seriousness, severity, relationship to study treatment, and adverse event outcomes were made by the Applicant and coded using MedDRA version 20.1.
All clinical safety datasets were acceptable for analysis. During the review cycle, the Applicant submitted an updated laboratory (ADLB) dataset with baseline and post baseline flags requested by the reviewer.
The Applicant analyzed AE preferred terms (PT) by primary system organ class (SOC) and identified SOCs containing PTs reported for ≥ 5% of patients. The translation of verbatim terms to PTs was appropriate. PTs for elevated aminotransferases were split within the "Investigations" SOC.
The sNDA included a summary of clinical safety data for anidulafungin that included the pediatric study A8851008, two small PK/safety studies (Duke IIR study and a Phase 1/2 study), and the results of a search of their safety database to identify postmarket AEs for pediatric patients receiving anidulafungin.

Routine Clinical Tests

Per protocol, hematology laboratory tests included, red blood cell (RBC), reticulocyte (absolute or percent), white blood cell, differential WBC cell count (absolute or percent %), and platelet count. Hemoglobin and hematocrit test results were not collected as per protocol. Chemistry tests included electrolytes, blood urea nitrogen, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, albumin, glucose, calcium, and magnesium. For female subjects of childbearing potential, a urine or serum pregnancy test was performed at screening, EOIVT, EOT, and at the 6-week follow-up visit.

10.4. Safety Results

10.4.1. Deaths

Deaths in the safety population are summarized in Table 10-2. Eleven patients (16.2%) died; 8 deaths occurred during the study and 2 deaths occurred outside the safety-reporting period, after the 6-week follow-up visit. An additional death of unknown cause was first reported to the

Applicant at 12 months after the end of anidulafungin IV therapy (EOIVT) and after the final clinical study report (CSR) was issued and was not included in the Applicant's analyses of death. An analysis of deaths by country and study site revealed that approximately 50% of the deaths occurred in Brazil and 4 deaths were at one Brazilian (b) (6)

The mortality rate was higher in the oldest age group with 7 deaths reported in the 5 to < 18y age group, 1 death in the 2 to < 5y age group, and 3 deaths in the 1 month to < 2y age group. Most of the deaths occurred posttreatment with anidulafungin except for a one 3-year-old, neutropenic patient with candidemia who received anidulafungin on Day 1 and died of septic shock on the same day.

Deaths were associated with invasive candidiasis in 2 patients or complications related to the patients' underlying diseases such as bacteremia/ septic shock, respiratory or multiorgan failure, intracranial hemorrhage, or progression of underlying malignancy. None of the deaths were attributed to treatment with anidulafungin.

Table 10-2 A8851008: Summary of Deaths - Safety Population

Unique Subject Identifier	Age at enrollment / Sex/Country	Study Day of Death (Day of last anidulafungin dose)	Primary Cause of Death	Invasive *Candida* species at baseline
(b) (6)	3 years / M/ BRA	1 (1)	septic shock / candidemia	*C. albicans*
	6 years / M/ KOR	4 (3)	acute respiratory distress syndrome / pneumonia	*C. tropicalis*
	12 years / F/ BRA	4 (3)	acute respiratory failure / pneumonia	*C. tropicalis*
	5 years / M/ BRA	12 (10)	medulloblastoma / disease progression	*C. albicans*
	17 years / M/ TWN	18 (12)	sepsis / *S. maltophilia* septicemia	*C. tropicalis*
	7 years / M/ TWN	20 (1)	septic shock / candidemia	*C. albicans*
	31 months / F/ TWN	36 (10)	intracranial hemorrhage	*C. guilliermondii*
	16 months / M/ USA	40 (7)	multiorgan failure	*C. parapsilosis*
	4 years / F/BRA	81[a] (28)	sepsis /respiratory failure	*C. albicans*
	11 years / F/BRA	996[a] (14)	Ewing sarcoma / disease progression	*C. parapsilosis*
	1 months / M/BRA	?[a]	unknown	No results

Unique Subject Identifier	Age at enrollment / Sex/Country	Study Day of Death (Day of last anidulafungin dose)	Primary Cause of Death	Invasive *Candida* species at baseline

Source: OCS Analysis Studio V.13, Listing Tool.
Subjects - Dataset: Demographics; Filter: SAFFL = 'Y'. BRA: Brazil, TWN: Taiwan, KOR: Korea, USA: United States of America.
[a] Death occurred outside the study reporting period, i.e. after the 6-week follow-up period.
*Subject (b) (6) died 3 years after the study (Day 996) and was 14 years of age at time of her death.
† Subject was aged 1 month at enrollment on (b) (6); his death was reported on (b) (6) but the exact age at death or date of death is unknown. The patient had a history of chronic kidney insufficiency and was on intermittent hemodialysis.

Clinical reviewer's comment: *The reviewer assessed the case narratives for all deaths and none of the deaths appeared to be related to anidulafungin.* Candidemia is associated with up to 47% attributable mortality[19,20,21] and this is even higher
among persons with septic shock.[22] *The overall mortality rate of 16.2% in the pediatric population (33% were neutropenic) was lower than the mortality rate of 22.8% in the anidulafungin arm of the phase 3 controlled trial (VER002-9) in mostly non-neutropenic adult patients with candidemia and other forms of invasive candidiasis.*[23] *No definitive conclusions can be made regarding differences in mortality rates based on a cross-study comparison due to the differences underlying diseases, levels of immunosuppression in the two study populations, and changes over time in intensive care management.*

10.4.2. Serious Adverse Events

Table 10-3 summarizes all reported SAEs that occurred during anidulafungin or fluconazole treatment in the safety population. Treatment-emergent SAEs were reported in 30 (44.1%) patients. SAEs occurring in two or more subjects were infectious complications such as *Staphylococcus* bacteremia, sepsis/ septic shock, febrile neutropenia, urinary tract infection, pneumonia, device-related infection, and herpes zoster. The majority of reported SAEs had an outcome of recovered/resolved except for five SAEs which were unrelated to anidulafungin, i.e., brachiocephalic vein thrombosis, *E. coli* infection, gastrointestinal hemorrhage, metabolic acidosis, and pneumonia. SAEs by study subject are summarized in Table 17 4.

[19] Pfaller M, Neofytos D, Diekema D, et al. Epidemiology and outcomes of candidemia in 3648 patients: data from the Prospective Antifungal Therapy (PATH Alliance(R)) registry, 2004–2008. Diagn Microbiol Infect Dis 2012; 74:323–31.
[20] Diekema D, Arbefeville S, Boyken L, et al. The changing epidemiology of healthcare-associated candidemia over three decades. Diagn Microbiol Infect Dis 2012; 73:45–8.
[21] Morgan J, Meltzer MI, Plikaytis BD, et al. Excess mortality, hospital stay, and cost due to candidemia: a case-control study using data from population-based candidemia surveillance. Infect Control Hosp Epidemiol 2005; 26:540–7.
[22] Kollef M, Micek S, Hampton N, et al. Septic shock attributed to *Candida* infection: Importance of Empiric Therapy and Source Control. Clin Infect Dis 2012; 54:1739–46.
[23] ERAXIS® USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021632s026lbl.pdf

Three SAEs were possibly associated with anidulafungin treatment and included seizure (n=1), diarrhea (n=1), and increased aminotransferases (n=1). A 5-year-old male and 3-month-old female experienced SAEs of increased hepatic aminotransferases and diarrhea, respectively, which were attributed to anidulafungin; both SAEs were categorized as severe and led to the discontinuation of anidulafungin. A 17-year-old male, with a history of a seizure disorder, experienced a severe seizure on Day 12 of anidulafungin treatment and had recovered by Day 14. Treatment with anidulafungin was continued throughout the event and no further seizures occurred in this patient. Two additional subjects who had seizures and were categorized as non-serious AEs are discussed in section 10.5.5.

The SAEs of seizure and diarrhea resolved within 2 to 6 days. The SAE of elevated aminotransferases did not resolve and were elevated at the time of the patient's death from progression of medulloblastoma.

Table 10-3 A8851008: Serious Adverse Events by Preferred Term (Incidence ≥ 1.5%) – Safety Population

		ANIDULAFUNGIN N=68		FLUCONAZOLE n=31*	
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**
Blood and lymphatic system disorders	Coagulopathy	1	1.5%	.	.
	Febrile neutropenia	.	.	2	6.5%
	Pancytopenia	1	1.5%	.	.
Gastrointestinal disorders	Diarrhea	1	1.5%	.	.
	Gastrointestinal hemorrhage	.	.	1	3.2%
	Pancreatic pseudocyst	1	1.5%	.	.
General disorders and administration site conditions	General physical health deterioration	.	.	1	3.2%
Infections and infestations	Abdominal sepsis	1	1.5%	.	.
	Catheter site infection	.	.	1	3.2%
	Device related infection	1	1.5%	1	3.2%
	Escherichia infection	1	1.5%	.	.
	Herpes zoster	.	.	2	6.5%
	Lower respiratory tract infection	.	.	1	3.2%
	Meningitis	1	1.5%	.	.
	Oral herpes	.	.	1	3.2%
	Pharyngitis streptococcal	.	.	1	3.2%
	Pneumonia	1	1.5%	1	3.2%
	Sepsis	.	.	2	6.5%
	Septic shock	2	2.9%	.	.
	Staphylococcal bacteremia	.	.	3	9.7%
	Streptococcal sepsis	1	1.5%	.	.
	Urinary tract infection	2	2.9%	.	.
Injury, poisoning and procedural complications	Unintentional medical device removal	1	1.5%	.	.
Investigations	Aspiration bronchial	1	1.5%	.	.

		ANIDULAFUNGIN N=68		FLUCONAZOLE n=31*	
Body System or Organ Class	**Dictionary-Derived Term**	**Count**	**%**	**Count**	**%**
	Transaminases increased	1	1.5%	.	.
Metabolism and nutrition disorders	Hypoglycemia	.	.	1	3.2%
	Metabolic acidosis	1	1.5%	.	.
Nervous system disorders	Hemorrhage intracranial	1	1.5%	.	.
	Seizure	1	1.5%	.	.
Psychiatric disorders	Mental status changes	.	.	1	3.2%
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	1	1.5%	.	.
	Acute respiratory failure	1	1.5%	.	.
	Respiratory distress	1	1.5%	.	.
	Respiratory failure	1	1.5%	.	.
Vascular disorders	Brachiocephalic vein thrombosis	.	.	1	3.2%

Source: JMP Clinical v7.0; ADAE and ADSL datasets; Filters: SAFFL=Y, TRTEMFL=Y.
* After a minimum of 10 days of anidulafungin IV treatment, 31 of the patients were switched to oral fluconazole to complete antifungal treatment.

Clinical reviewer's comment: *Elevated transaminases and diarrhea are known adverse reactions associated with anidulafungin. An attribution of seizure to anidulafungin was confounded by the patient's underlying seizure disorder; however, an association with anidulafungin cannot be completely ruled out. Elevated transaminases, diarrhea, and seizure are labeled adverse reactions in the ERAXIS® USPI. No other SAEs were assessed as related to either anidulafungin or fluconazole treatment.*

10.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 8-2 summarizes the disposition of the 70 patients enrolled in Study A8851008. Forty-eight patients (70.6%) completed anidulafungin treatment. Among the 20 patients (29.4%) who discontinued study drugs, 7 patients (10.3%) discontinued treatment due to an adverse event, anidulafungin (n=6) and fluconazole (n=1).

Table 10-4 summarizes clinical details for the 7 patients (10.3%) who discontinued study drugs. Vomiting, diarrhea, generalized pruritus, and increased transaminases were considered treatment-related and led to the discontinuation of anidulafungin in 6 (8.8%) patients. One patient discontinued fluconazole due to the onset of sepsis and was switched to another systemic antifungal drug.
There were no other reported allergic symptoms associated with the TEAE of generalized pruritus. All the TEAEs resolved except for one TEAE of severe increased transaminases in a 5-year-old male with progression of medulloblastoma (discussed in section 10.5).

Table 10-4 A8851008: Treatment Emergent Adverse Events Leading to Discontinuation of Anidulafungin or Fluconazole

Unique Subject Identifier	Sex / Race	Age	Dictionary-Derived Term	Day Start/ End	Study Phase/Tx	Severity	Outcome of TEAE	Causality	Serious Event
(b) (6)	F / White	34m	Vomiting	10 / 11	Active/ Anidula	mild	recovered/resolved	possibly related	N
	F / White	28m	ALT increased	4 / 41	Active/ Anidula	moderate	recovered/resolved	related	N
			AST increased	4 / 41	Active/ Anidula	moderate	recovered/resolved with sequelae	related	N
	M / Asian	17y	Sepsis	16 / 18	Active/ Flu	severe	recovered/resolved	not related	Y
	M / Asian	7y	Pruritus generalized	1 / 2	Active/ Anidula	moderate	recovered/resolved	related	N
	M / Other	5y	Transaminases increased	10 / 12	Active/ Anidula	severe	not recovered/ not resolved	related	Y
	F / White	3m	Diarrhea	1 / 6	Active/ Anidula	severe	recovered/resolved	related	Y
	M / White	1m	Transaminases increased	14 / 22	Active/ Anidula	mild	recovered/resolved	not related	N

Source: OCS Analysis Studio, Listing Table Tool.
Subjects - Dataset (ADSL): Demographics; Filter: SAFFL = 'Y'.
Events - Dataset (ADAE): Adverse Events; Filter: PERMDIFL = 'Y'. Anidula: Anidulafungin; Flu: Fluconazole; Tx: Antifungal Treatment.

Clinical reviewer's comment: *Vomiting, diarrhea, pruritus, and increased transaminases are known to be associated with anidulafungin treatment in adults and are listed in the ERAXIS® USPI.*

10.4.4. Significant Adverse Events

The severity of AEs by age group are summarized in Figure 10-1. Severe TEAEs were reported in 28 (41.2%) patients and occurred more frequently in the 5 to 17 age group than in younger patients.

Six treatment-related severe TEAEs were reported in 5 subjects (7.4%) and included neutropenia, gastrointestinal hemorrhage, increased transaminases, hyponatremia, myalgia, and diarrhea. Increased aminotransferases and diarrhea resulted in permanent discontinuation of anidulafungin in two patients. Anidulafungin was continued in the patients who experienced either myalgia (resolved) or hyponatremia (ongoing at the time of last data collection). Neutropenia and gastrointestinal hemorrhage occurred in one patient on fluconazole treatment. One patient developed acute pancreatitis/ severe hyperbilirubinemia/ ocular

icterus at 11 days post treatment with anidulafungin; these TEAEs were deemed not to be related to anidulafungin.

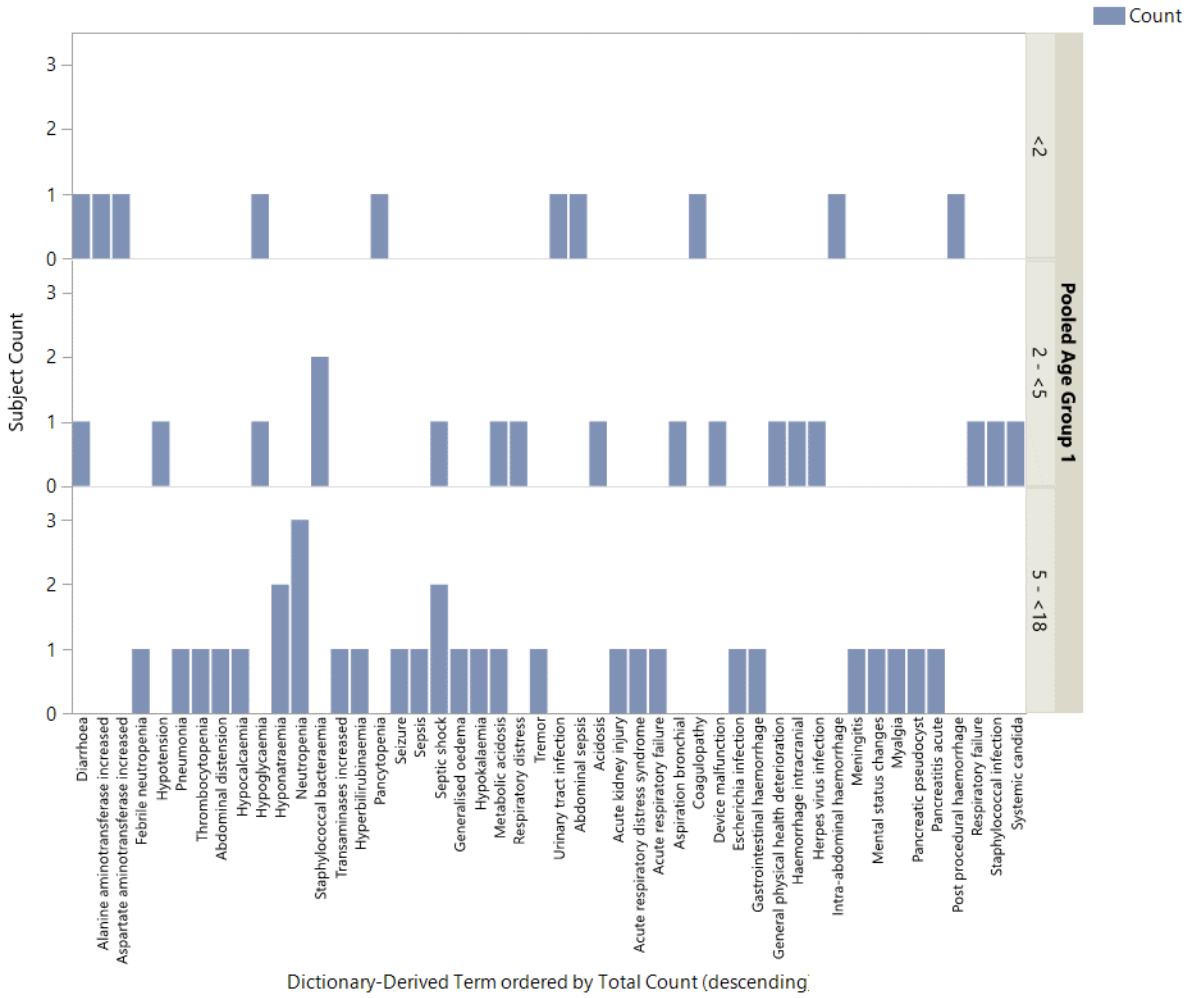
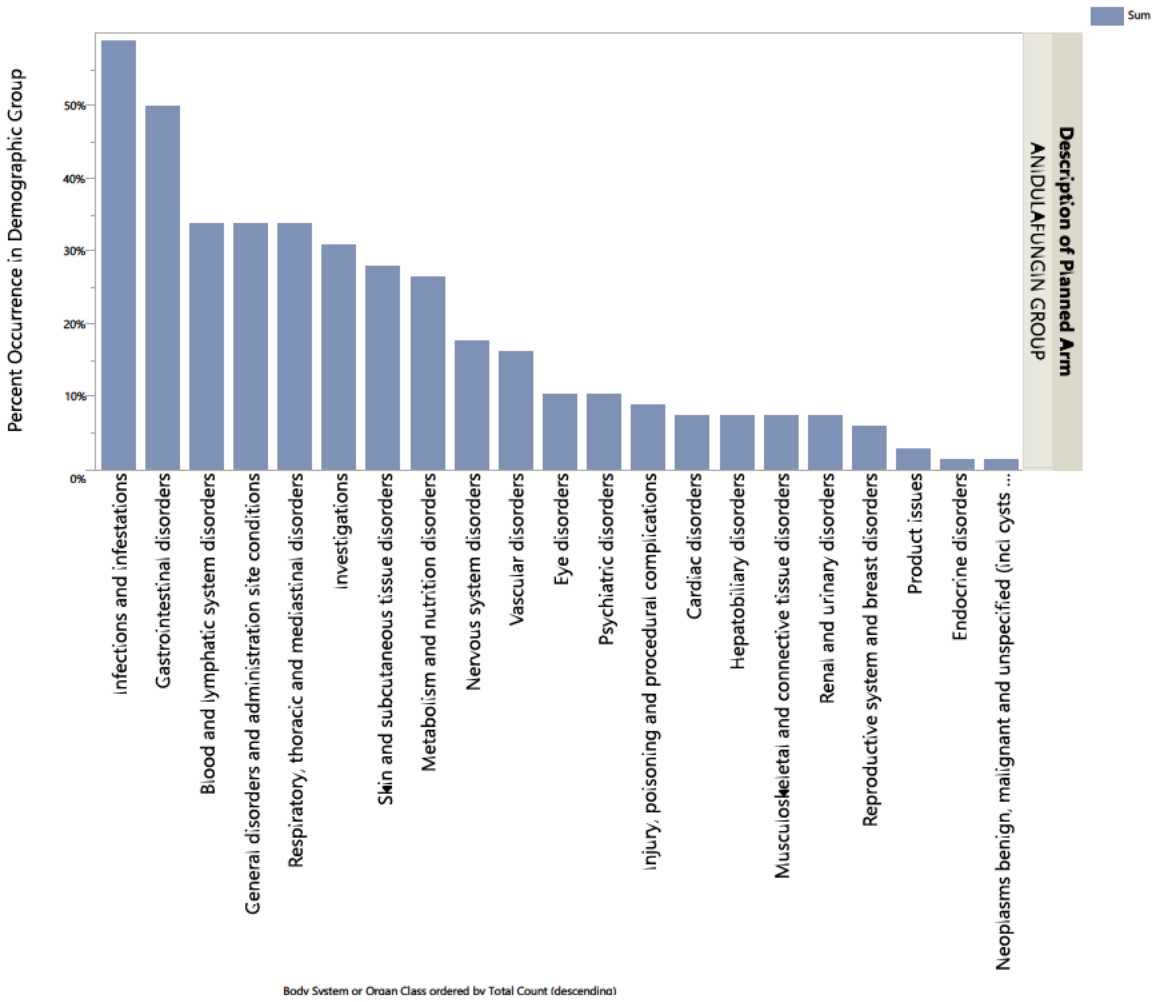


Figure 10-1 A8851008: Severe TEAEs by Preferred Term and Age Group – Safety Population

10.4.5. Treatment Emergent Adverse Events and Adverse Reactions

TEAEs categorized by SOC are summarized in Figure 10-2 and Table 10-6. The Infections/Infestations SOC was most frequently affected (~60% of subjects) with pneumonia and bacteremia as the most common TEAEs. Gastrointestinal Disorders was the next most common affected SOC (~50% of subjects) with vomiting and diarrhea as the most frequently reported TEAEs. TEAEs from these two SOCs were also the most common across the three age groups, < 2 years, 2 to < 5 years, and 5 to ≤18 years.



Source: JMP Clinical v7.0: ADSL and ADAE datasets; Safety Population: SAFFL; Treatment emergent flag: TRTEMFL

Figure 10-2 A8851008: Treatment Emergent Adverse Events by System Organ Class

A total of 422 TEAEs (i.e., AEs reported during active treatment and up to 30 days after the last dose of study drug) were reported in 66 (97.1%) patients. The largest proportion of TEAEs occurred in the 5 to < 18 years age group. Severe TEAEs were reported in 28 (41.2%) subjects; 6 of these events were assessed as treatment-related. A total of 7 (10.3%) patients withdrew from the study due to TEAEs, see section 10.4.3.

Table 10-5 A8851008: Categorization of TEAEs by Age Group - Safety Population

	1 m to < 2yrs N=19 (%)	2 to < 5 yrs N=19 (%)	5 to < 18yrs N=30 (%)	Total N=68 (100%)
Total No. of Subjects with TEAEs	17 (89.5)	19 (100)	30 (100)	66 (97.1%)
No. of TEAEs*	88	136	198	422
Subjects with SAEs	7 (36.8)	10 (52.6)	13 (43.3)	30 (44.1)

	1 m to < 2yrs N=19 (%)	2 to < 5 yrs N=19 (%)	5 to < 18yrs N=30 (%)	Total N=68 (100%)
Subjects with severe TEAEs	7 (36.8)	8 (42.1)	13 (43.3)	28 (41.2)
Subjects discontinued treatment due to TEAE	2(10.5)	2(10.5)	2(6.7)	7 (10.3)
Anidulafungin	*2*	*2*	*2*	*6*
Fluconazole	*0*	*0*	*0*	*1*
Dose reduced or temporarily discontinued	0	0	2 (6.7)	2 (2.9)
Anidulafungin	*0*	*0*	*1*	*1*
Fluconazole	*0*	*0*	*1*	*1*

*Except for the "Number of TEAEs" subjects are counted only once in each row.
Source: ADSL and ADAE datasets, JReview v 13.1

TEAEs occurring in 3 or more patients (≥ 4%) in the safety population are summarized in Table 10-6. The analysis includes TEAEs (all-causality) that started on or after the first dose of anidulafungin for all patients in the safety population through Week 6 of follow up and therefore includes the patients who received fluconazole as follow-on treatment.
TEAEs were reported in 66 (97%) patients. Vomiting (24%), diarrhea (22%), pyrexia (19%), and increases in aminotransferases (19%) were the most commonly reported TEAEs among all patients.

Table 10-6 A8851008: Treatment emergent adverse events occurring in 3 or more subjects (≥ 4%) – Safety Population

	Safety Population (N=68)
Any TEAE	**66 (97%)**
Infections and infestations	**40 (58.8)**
Pneumonia	5 (7.4)
Staphylococcal bacteremia	4 (5.9)
Upper respiratory tract infection	4 (5.9)
Bacteremia	3 (4.4)
Device related infection	3 (4.4)
Lower respiratory tract infection	3 (4.4)
Sepsis	3 (4.4)
Septic shock	3 (4.4)
Gastrointestinal disorders	**34 (50.0)**
Vomiting	16 (23.5)
Diarrhea	15 (22.1)
Abdominal pain	6 (8.8)
Abdominal distension	4 (5.9)
Nausea	4 (5.9)

	Safety Population (N=68)
Blood and lymphatic system disorders	**23 (33.8)**
Anemia	9 (13.2)
Febrile neutropenia	5 (7.4)
Thrombocytopenia	5 (7.4)
Neutropenia	4 (5.9)
Leukopenia	3 (4.4)
Pancytopenia	3 (4.4)
Thrombocytosis	3 (4.4)
General disorders and administration site conditions	**23 (33.8)**
Pyrexia	13 (19.1)
Respiratory, thoracic and mediastinal disorders	**23 (33.8)**
Epistaxis	9 (13.2)
Investigations	**21 (30.9)**
Aminotransferases increased†	13 (19.1)
Skin and subcutaneous tissue disorders	**19 (27.9)**
Rash*	6 (8.8)
Metabolism and nutrition disorders	**18 (26.5)**
Hypocalcemia	4 (5.9)
Hypoglycemia	4 (5.9)
Hyponatremia	4 (5.9)
Hypoproteinemia	3 (4.4)
Nervous system disorders	**12 (17.6)**
Headache	7 (10.3)
Seizure	3 (4.4)
Vascular disorders	**11 (16.2)**
Hypotension	5 (7.4)
Psychiatric disorders	**7 (10.3)**
Agitation	4 (5.9)
Hepatobiliary disorders	**5 (7.4)**
Hyperbilirubinemia	3 (4.4)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Table Section 1 - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'; Percent Threshold: >= 4%.
* rash includes rash and rash generalized
†Aminotransferases increased included preferred terms: ALT increased, AST increased, transaminases increased, Liver function abnormal, liver function test increased.

Clinical reviewer's comment: *The reviewer compared the common TEAEs reported in the pediatric patients treated with anidulafungin with the adverse reactions listed for adults in the phase 3, registrational candidemia/invasive candidiasis trial, VER002-9 described in the current ERAXIS® USPI .*[15]

Cross-study comparisons are difficult due to differences in study design and patient populations, but general observations regarding drug safety can be made. No new TEAEs related to anidulafungin were identified in pediatric patients in study A8851008. TEAEs were similar among pediatric and adult patients, for example, vomiting and diarrhea were common in both study populations. Hepatobiliary adverse events and hepatic laboratory investigations are discussed in sections 10.4.6 and 10.5.1.

Table 10-7 presents TEAEs at a ≥ 5% incidence in patients by age group who received anidulafungin. The analysis includes TEAEs that started on or after first dose of anidulafungin through the 6-week follow-up for patients who did not receive oral fluconazole, and those TEAEs that started between first dose and last dose of anidulafungin for patients who were switched to oral fluconazole. TEAEs were reported in 55 patients (81%) and were more frequent in the youngest age group, 1 month to < 24 months of age. TEAEs related to anidulafungin such as diarrhea, increased aminotransferases, and rash occurred at higher rates in patients less than 2 years of age than in older children.

Table 10-7 A8851008: Treatment emergent adverse events* occurring in ≥ 5% of patients by age group treated with anidulafungin through Week 6 follow-up - Safety Population

	Pediatric Age Groups Treated with Anidulafungin			
Treatment Emergent Adverse Event	**1 month to <2y n=19**	**2 to <5y n=19**	**5 to <18y n=30**	**Totals N=68**
Subjects with at least 1 TEAE	**17 (89.5%)**	**14 (73.7%)**	**24 (80.0%)**	**55 (80.9%)**
Blood and lymphatic system disorders	**9 (47.4%)**	**3 (15.8%)**	**4 (13.3%)**	**16 (23.5%)**
Anemia	5 (26.3%)	2 (10.5%)	0	7 (10.3%)
Thrombocytopenia	2 (10.5%)	1 (5.3%)	1 (3.3%)	4 (5.9%)
Gastrointestinal disorders	**8 (42.1%)**	**8 (42.1%)**	**12 (40.0%)**	**28 (41.2%)**
Abdominal pain†	0	4 (21.1%)	2 (6.7%)	6 (8.8%)
Diarrhea	4 (21.1%)	2 (10.5%)	5 (16.7%)	10 (14.7%)
Vomiting	4 (21.1%)	5 (26.3%)	2 (6.7%)	11 (16.2%)
General disorders and administration site conditions	**5 (26.3%)**	**6 (31.6%)**	**9 (30.0%)**	**20 (29.4%)**
Pyrexia	4 (21.1%)	3 (15.8%)	5 (16.7%)	12 (17.6%)
Investigations	**4 (21.1%)**	**4 (21.1%)**	**8 (23.3%)**	**16 (22.1%)**
ALT increased	2 (10.5%)	2 (10.5%)	2 (6.7%)	6 (8.8%)
AST increased	2 (10.5%)	1 (5.3%)	1 (3.3%)	4 (5.9%)
Transaminases incr. (ALT or AST)	1 (5.3%)	0 (0.0%)	1 (3.3%)	2 (2.9%)
Abnormal liver function tests (ALT incr.)	0	0	1 (3.3%)	1 (1.5%)
Total of increased aminotransferases	5 (26.3%)	3 (15.8%)	5 (16.7%)	13 (19.1)
Metabolism and nutrition disorders	**3 (15.8%)**	**4 (21.1%)**	**6 (20.0%)**	**13 (19.1%)**
Hypoglycemia	1 (5.3%)	2 (10.5%)	1 (3.3%)	4 (5.9%)
Respiratory, thoracic and mediastinal disorders	**5 (26.3%)**	**5 (16.7%)**	**5 (26.3%)**	**15 (22.1%)**
Epistaxis	1 (5.3%)	2 (10.5%)	3 (10.0%)	6 (8.8%)
Skin and subcutaneous tissue disorders	**6 (31.6%)**	**5 (26.3%)**	**5 (13.3%)**	**16 (23.5%)**
Rash‡	3 (15.8%)	1 (5.3%)	2 (6.7%)	6 (8.8%)

Source: ADSL and ADAE datasets, JReview v 13.1

*Analysis includes all treatment emergent adverse events, including those that started on or after first dose of anidulafungin through 6-week follow-up for patients who did not receive oral fluconazole, and those that started between first dose and last dose of anidulafungin for patients who received oral fluconazole. A patient who experienced multiple events within a Body

System or preferred term was counted one time for that class, one time for the preferred term and one time for subjects with at least one adverse events.
† Includes such the preferred terms: abdominal pain and abdominal pain upper
‡ Includes the preferred terms: rash and rash generalized.

10.4.6. Laboratory Findings

Sixty-seven patients (98.5%) had at least one post baseline abnormal laboratory result regardless of their baseline results. Patients who had a baseline value and at least one post baseline value for selected hematology, chemistry and hepatic laboratory parameters were further analyzed for the degree of shift from baseline.

Hepatic Enzymes Abnormalities
In the study, 18 patients (26.9%) had ALT >3 × ULN, 17 patients (25.4%) had AST > 3× ULN, and 11 patients (16.4%) had total bilirubin ≥ 1.5 × ULN. In the laboratory dataset (ADLB), (b) (4) patients had values for "change from baseline" for ALT and total bilirubin levels, respectively, and patients with missing values for this variable were excluded from the laboratory shift tables in this review.

Table 10-8 summarizes post baseline shifts in ALT. Most of the patients had abnormal baseline ALT levels. Post baseline increases in ALT levels ranged from >3x up to > 20x ULN. Among subjects with ALT in the normal range at baseline, post baseline ALT elevations >3x ULN were observed in 6 patients (9.5%). ALT levels returned to baseline values or within the normal range in almost all patients except for a 5-year-old male patient who had an elevated ALT > 20 x ULN which started on Day 10 and was present at the time of his death on Day 12 due to progression of medulloblastoma.

Table 10-8 A8851008: Maximum Post Baseline Shifts in ALT Level Categories

	Maximum Post Baseline Shifts in ALT Level Categories - Postbaseline							
ALT Categories at Baseline	**<LLN**	**>=LLN to <=ULN**	**>ULN to <=3xULN**	**>3xULN to <=5xULN**	**>5xULN to <=10xULN**	**>10xULN to <=15xULN**	**>20xULN**	**Total No. Subjects, n/N (%)**
	2 (3.2%)	**12(19.0%)**	**31(49.2%)**	**8(12.7%)**	**7 (11.1%)**	**1 (1.6%)**	**2 (3.2%)**	**63 (100.0%)**
<LLN	2 (3.2%)	0	1 (1.6%)	0	0	0	0	3 (4.8%)
≥LLN to ≤ULN	0	7 (11.1%)	11 (17.5%)	3 (4.8%)	2 (3.2%)	0	1 (1.6%)	24 (38.1%)
>ULN to ≤3xULN	0	5 (7.9%)	16 (25.4%)	3 (4.8%)	2 (3.2%)	0	0	26 (41.3%)
>3xULN to ≤5xULN	0	0	3 (4.8%)	2 (3.2%)	2 (3.2%)	1 (1.6%)	1 (1.6%)	9 (14.3%)
>5xULN to ≤10xULN	0	0	0	0	1 (1.6%)	0	0	1 (1.6%)

Source: ADLB dataset, JReview v. 13.1; The analysis included ALT values where a "change from baseline" value was not missing

AST: Seventeen (25.8%) patients had AST >3 × ULN (AST shift table is not shown). Two patients (2.9%) had elevated AST values that did not return to baseline or normal range by the final study visit and were not trending towards normal ranges by the final visit.

Discontinuation of anidulafungin due to elevated ALT and/or AST > 10× ULN or elevated total bilirubin occurred in three subjects during the treatment period. These cases are described under hepatic adverse events in section 10.5.

Clinical reviewer's comments: *Elevated aminotransferase levels are associated with the echinocandin class of antifungals and are expected TEAEs. Elevated aminotransferase levels occurred at slightly lower rates in the phase 3 candidemia/invasive candidiasis trial in adults, VER002-9. In VER002-9, 20 (15.7%) anidulafungin-treated patients had an ALT value >3x ULN, AST value > 3x ULN, and/or an ALT value >3x ULN and a total bilirubin value > 1.5x ULN (on the same date) at any timepoint during the trial.*

Table 10-9 summarizes the post baseline shifts in total bilirubin levels. Maximum post baseline increases in total bilirubin level >2 x ULN were observed in 10 patients (16.1%). Among subjects with normal total bilirubin levels at baseline, post baseline elevations of > 2x were observed in 3 (1.6%) patients. Two male patients, 7 and 17 years of age, had elevated total bilirubin values that did not return to normal ranges or baseline by the final study visit.

Table 10-9 A8851008: Maximum Post Baseline Shifts in Total Bilirubin Level Categories

	Max. Total Bilirubin Level Categories - Postbaseline				
Total Bilirubin Categories at Baseline	**>=LLN to <=ULN,**	**>ULN to <=2xULN,**	**>2xULN to <=5xULN,**	**>5xULN,**	**Total No. Subjects, n/N (%)**
	50 (80.6%)	**2 (3.2%)**	**9 (14.5%)**	**1 (1.6%)**	**62 (100.0%)**
<LLN	9 (14.5%)	0	0	0	9 (14.5%)
>=LLN to <=ULN	38 (61.3%)	1 (1.6%)	2 (3.2%)	1 (1.6%)	42 (67.7%)
>ULN to <=2xULN	3 (4.8%)	1 (1.6%)	3 (4.8%)	0	7 (11.3%)
>2xULN to <=5xULN	0	0	4 (6.5%)	0	4 (6.5%)

Source: ADLB dataset. J Review v. 13.1. The analysis included total bilirubin values where a change from baseline value was not missing.

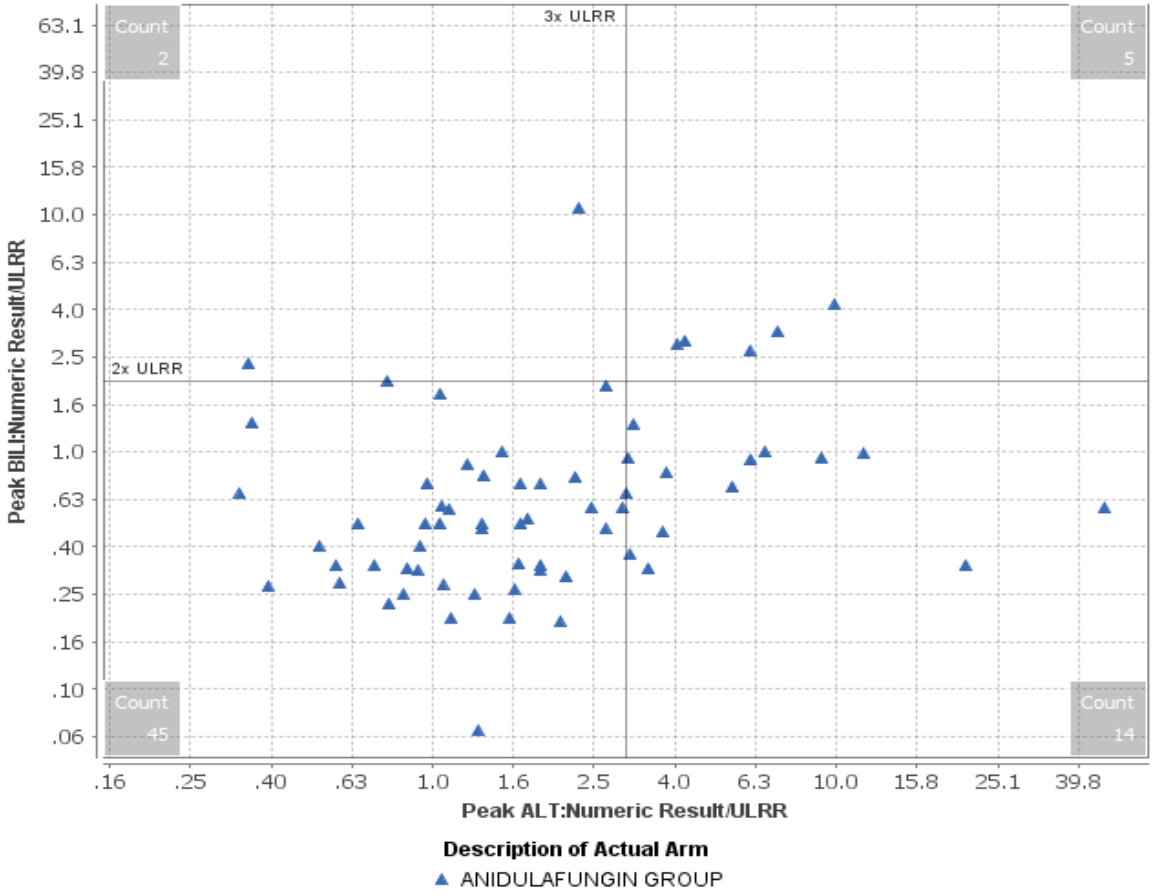
Potential Hy's Law Cases

Abnormal values in ALT and/or AST level concurrent with abnormal elevations in total bilirubin, and in the absence of other causes of liver injury, were considered potential cases of drug-induced liver injury (DILI) or potential Hy's Law cases.

In the study protocol, the threshold of laboratory abnormalities for a potential case of drug-induced liver (DILI) injury were:
A. Subjects with ALT or AST baseline values within the normal range who subsequently present with ALT or AST ≥3 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, OR

B. Subjects with pre-existing ALT or AST baseline values above the normal range who subsequently present with ALT or AST ≥2 times the baseline values and ≥3 x ULN, or ≥8 x ULN (whichever is smaller) concurrent with a total bilirubin of ≥ 2 x ULN and increased by one upper limit of normal over baseline or >3 x ULN (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase ≤2 x ULN or not available.

ALT and total bilirubin results were analyzed to identify patients with biochemical data that fulfilled Hy's Law criteria, see Figure 10-3. Five patients (Subjects (b) (6) fulfilled the biochemical criteria for Hy's Law, i.e., ALT > 3x ULN, total bilirubin > 2x ULN and alkaline phosphatase ≤2x ULN. A review of the cases narratives indicated that three patients (b) (6) were potential Hy's Law cases. In two subjects (b) (6), the elevated aminotransferases were present at baseline and were attributed to the patients' co-morbid diseases.

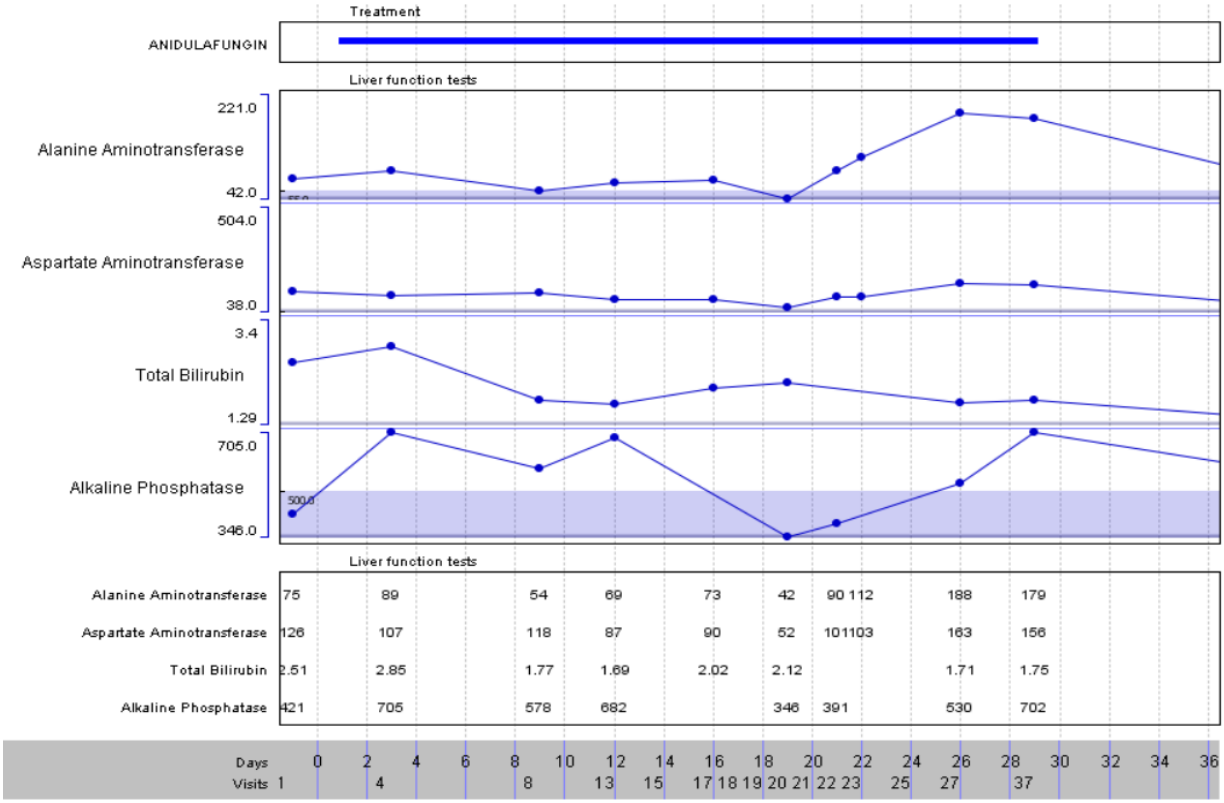


Source: Study A8851008, ADLB dataset; JReview v. 13.1

Figure 10-3 A8851008: Hy's Law Plot

Case narratives for the five patients are summarized below.

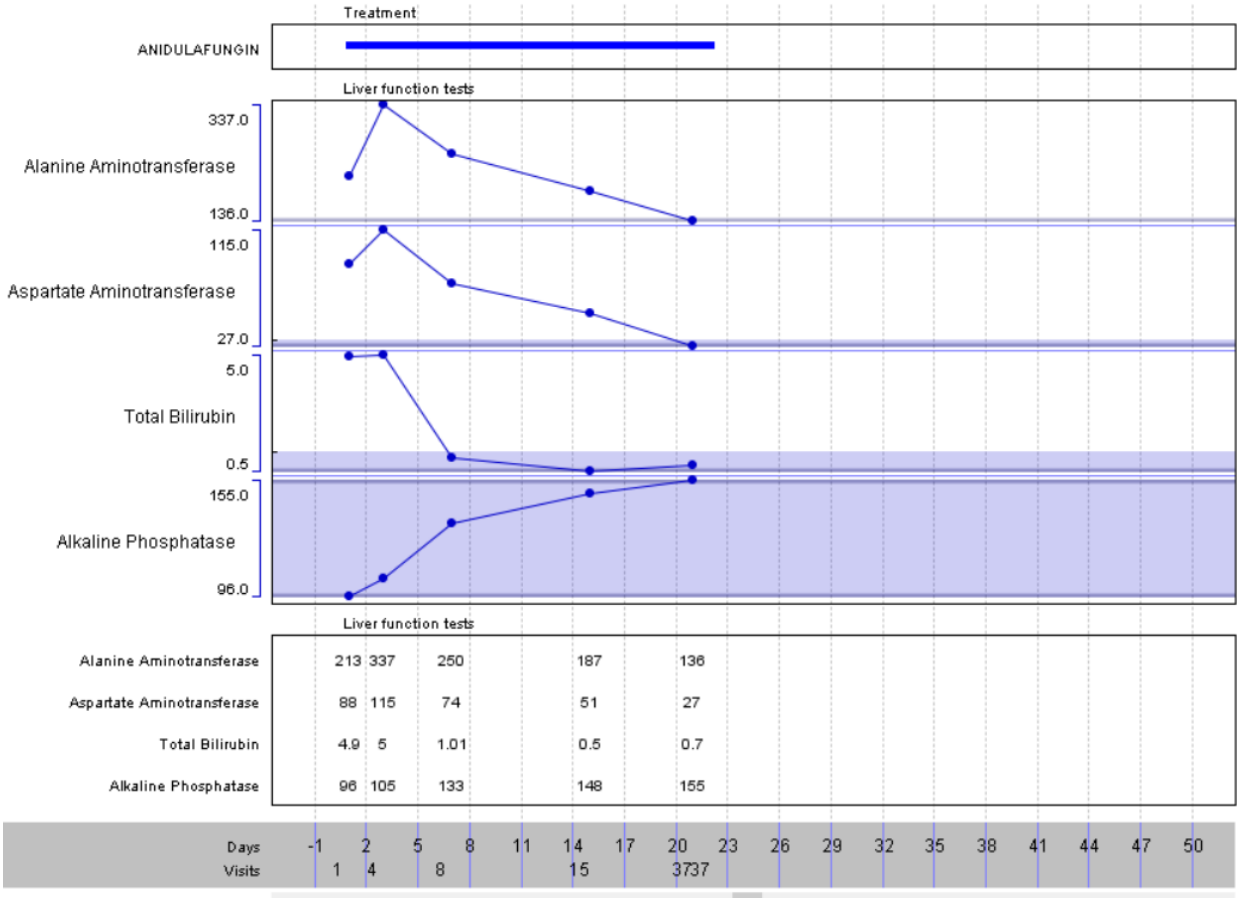
Subject (b) (6), a 4-year-old female (short bowel syndrome, colostomy, cholelithiasis), was diagnosed with *C. albicans* candidemia from a central venous catheter (CVC) and from a peripheral site on Day -5 and Day -3, respectively. She was diagnosed with aspiration pneumonia and respiratory failure on Day 17. She received anidulafungin from Day 1 through Day 28. Changes in hepatic enzymes levels from Day 1 through Day 30 of anidulafungin are shown in **Figure 10-4**. Aminotransferases, ALT 75 (0 - 55 IU/L), AST 126 (5 - 34 IU/L), and total bilirubin 2.51 mg/dl (0.1 - 1.2mg/dL) were elevated at baseline which was probably due to sepsis and multiple concomitant medications. Alkaline phosphatase was slightly elevated. Maximum elevations in ALT 188 (>3x ULN) and AST 163 (> 3x ULN), were observed on Day 26 of anidulafungin treatment; however, the total bilirubin 1.71mg/dL level was lower than the patient's baseline level. During the 28-day course of anidulafungin treatment, total bilirubin levels trended toward the normal range as ALT levels increased. ALT levels and total bilirubin were in the normal range at Day 42 when the patient was diagnosed with a recurrence of candidemia at 24 days post treatment with anidulafungin. ALT/AST and total bilirubin were elevated again at Day 81 (53 days post treatment with anidulafungin) associated with septicemia due to *Staphylococcus* sp. and *Candida albicans*. The patient died on Day 81 from sepsis and respiratory failure.



Source: ADLB dataset. JReview v. 13.1 Normal ranges for laboratory parameters are shaded in blue.

Figure 10-4 Subject (b) (6): Hepatic enzymes

Subject (b) (6) was a 17-year old white female (craniocerebral injury with diabetes insipidus due to vehicle accident) with *C. parapsilosis* candidemia from an arterial line. The baseline elevations in ALT 213 (10-34 IU/L), AST 88 (10-31 IU/L) and bilirubin 4.9 (0.3-1.2 mg/dL) attributed to sepsis and concomitant medications. On Day 3 of anidulafungin treatment, maximum elevations were ALT 337 (9x ULN), AST 115 (3x ULN), and total bilirubin 5 (4x ULN) and she was diagnosed with acute hepatitis. The patient was mechanically ventilated and receiving parenteral nutrition at the time of her diagnosis. All hepatic parameters improved on treatment with anidulafungin after Day 3 and were trending to the normal range at Day 21 of anidulafungin treatment. See **Figure 10-6**.

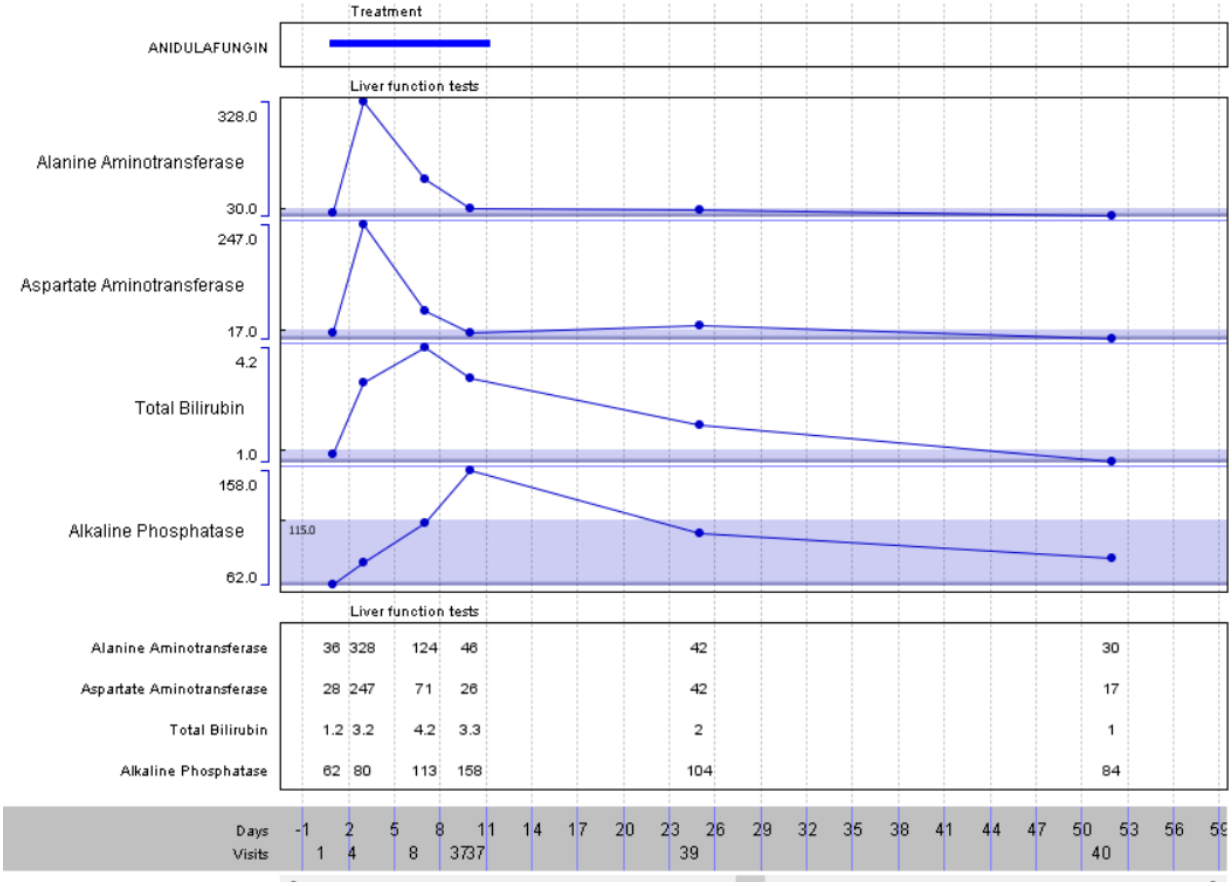


Source: ADLB dataset. JReview v. 13.1 Normal ranges for laboratory parameters are shaded in blue.

Figure 10-5 Subject (b) (6): Hepatic enzymes

Subject (b) (6), a 16-year old female (acute myeloid leukemia, atypical pneumonia), was diagnosed with *C. tropicalis* candidemia from a peripheral site and disseminated candidiasis with candiduria, liver abscess, and a focal skin lesion. Hepatic enzymes values from Day 1

through 30 of anidulafungin treatment are shown **Figure 10-8**. Baseline hepatic enzymes were in the normal range. Elevations in ALT 328 (6-46 IU/L), AST 247 (13-34 IU/L) and total bilirubin 3.2 (0.5- 1.3 mg/dL), with a normal alkaline phosphatase 62 (38-115 IU/L) were observed on Day 3 of anidulafungin treatment. ALT and AST values had normalized by Day 10 while she remained on anidulafungin. Total bilirubin levels peaked on Day 7 and then declined slowly and had normalized by the 6-week follow-up visit on Day 52. Anidulafungin was switched to amphotericin B on Day 10. The subject experienced septic shock due to disseminated candidiasis three days after the last dose of anidulafungin.



Source: ADLB dataset. JReview v. 13.1 Normal ranges for laboratory parameters are shaded in blue.

Figure 10-6 Subject (b) (6) Hepatic Enzymes

Clinical reviewer's comment: *These three cases were potential Hy's Law cases; however, there was no progression to serious hepatic injury. ALT and total bilirubin levels normalized on anidulafungin treatment suggesting that there may have been liver adaption to anidulafungin or other concomitant medication(s) causing hepatic injury.*

Two patients, Subject (b) (6), Subject (b) (6), had elevations in aminotransferases and total bilirubin; however, on further examination, they did not fulfill criteria for a potential Hy's Law case.
Subject (b) (6), a 1-month-old male (Trisomy 14, atrial septal defect), was diagnosed with *C. albicans* candidemia from a central venous line on Day -2. Hepatic transaminases and total bilirubin levels were elevated baseline. On Day 14 of anidulafungin treatment, maximum increases in hepatic transaminases were ALT 274 (13 - 45 IU/L), AST 2 81 (15- 60 IU/L), alkaline phosphatase < 2x ULN. Total bilirubin 1.6 (0-1.2 mg/dL) had decreased compared to the baseline level. Anidulafungin was permanently discontinued on Day 14 in response to this TEAE and treatment was switched to caspofungin from Day 15 to Day 17. At the Day 26 follow-up visit, ALT/AST/total bilirubin values were decreasing, and all parameters were in the normal range at the Day 54 follow up visit.

Clinical reviewer's comment: *This is not a potential Hy's Law case as the maximum bilirubin level was less than 1.5x ULN and was declining as ALT levels were increasing.*

Subject (b) (6) was a 3-year-old male subject (acute lymphocytic leukemia) with *C. guillermondii* candidemia. On Day 1, ALT 112 (0-36 IU/L), AST 109 (0-29 IU/L) and total bilirubin levels 1.37 (0.19856 – 0.9928 mg/dL) were elevated and then trended down toward normal range at the EOT visit on Day 26. ALT 152 and total bilirubin 2.9 peaked post treatment on Day 40. At the final Day 71 follow up visit, ALT 56 IU/L, AST 41 IU/L and total bilirubin 1.38 mg/dL were trending down toward the normal range. Alkaline phosphatase 799 (0-644 IU/L) was elevated on Day 1 but was otherwise normal throughout the study. Concomitant treatment with vincristine, methotrexate, cyclophosphamide, peg-aspargase, and cytarabine which probably contributed to the increases in hepatic enzymes in this patient. On Day 32 (6 days post treatment), a TEAE of mild hepatomegaly was reported and determined to be unrelated to study drug and had resolved by Day 56.

Clinical reviewer's comment: *This is not a potential Hy's Law case. ALT and bilirubin levels were mildly elevated prior to anidulafungin treatment and improved on anidulafungin treatment and peaked at 2 weeks post treatment.*

In summary, there is a reasonable possibility that anidulafungin contributed to elevations in hepatic aminotransferases and total bilirubin; however, attribution of causality is confounded by several factors such as abnormal hepatic enzymes at baseline, sepsis due to invasive candidiasis, and multiple concomitant medications.

Hematology

Most of the clinically significant laboratory abnormalities were observed in the hematological laboratory parameters, WBC, neutrophils, and absolute neutrophil count. Approximately 33% of the patients were neutropenic and 50% were thrombocytopenic at baseline. Abnormalities in hematological laboratory tests abnormalities were associated with sepsis and underlying co-

morbid disease such as hematological malignancies. The incidence of hematological laboratory abnormalities did not differ significantly between the three age groups, see Table 10-10.

Table 10-10 Incidence of Laboratory Test Abnormalities (without regard to baseline abnormalities) - Safety Population

			1 Month to <2 Years (N=19)		2 to <5 Years (N=19)		5 to <18 Years (N=30)		Overall (N=68)	
Number of subjects evaluable			19 (100)		19 (100)		30 (100)		68 (100)	
Number (%) with laboratory abnormalities			19 (100)		18 (94.7)		30 (100)		67 (98.5)	
Group Parameter	Units	Criteria	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Hematology										
Red blood cell count	$10^6/mm^3$	<0.8 × LLN	18	6 (33.3)	18	7 (38.9)	30	17 (56.7)	66	30 (45.5)
Reticulocytes count (%)	%	<0.5 × LLN	13	2 (15.4)	14	1 (7.1)	17	3 (17.6)	44	6 (13.6)
		>1.5 × ULN	13	5 (38.5)	14	7 (50.0)	17	5 (29.4)	44	17 (38.6)
Platelets	$10^3/mm^3$	<0.5 × LLN	19	5 (26.3)	18	7 (38.9)	30	14 (46.7)	67	26 (38.8)
		>1.75 × ULN	19	2 (10.5)	18	1 (5.6)	30	4 (13.3)	67	7 (10.4)
White blood cell count	$10^3/mm^3$	<0.6 × LLN	19	7 (36.8)	18	6 (33.3)	30	12 (40.0)	67	25 (37.3)
		>1.5 × ULN	19	1 (5.3)	18	2 (11.1)	30	7 (23.3)	67	10 (14.9)
Neutrophils (%)	%	<0.8 × LLN	18	4 (22.2)	18	7 (38.9)	30	11 (36.7)	66	22 (33.3)
		>1.2 × ULN	18	3 (16.7)	18	7 (38.9)	30	7 (23.3)	66	17 (25.8)
Basophils (%)	%	>1.2 × ULN	17	6 (35.3)	18	2 (11.1)	29	9 (31.0)	64	17 (26.6)
Lymphocytes (%)	%	<0.8 × LLN	18	7 (38.9)	18	10 (55.6)	30	16 (53.3)	66	33 (50.0)
		>1.2 × ULN	18	3 (16.7)	18	4 (22.2)	30	8 (26.7)	66	15 (22.7)
Monocytes (%)	%	>1.2 × ULN	18	9 (50.0)	18	9 (50.0)	30	14 (46.7)	66	32 (48.5)
Total neutrophils (Abs)	$10^3/mm^3$	<0.8 × LLN	18	8 (44.4)	17	7 (41.2)	28	13 (46.4)	63	28 (44.4)
		>1.2 × ULN	18	5 (27.8)	17	3 (17.6)	28	11 (39.3)	63	19 (30.2)
Basophils (Abs)	$10^3/mm^3$	>1.2 × ULN	17	2 (11.8)	17	1 (5.9)	26	2 (7.7)	60	5 (8.3)
Lymphocytes (Abs)	$10^3/mm^3$	<0.8 × LLN	18	8 (44.4)	17	10 (58.8)	27	15 (55.6)	62	33 (53.2)
		>1.2 × ULN	18	1(5.6)	17	1 (5.9)	27	3 (11.1)	62	5 (8.1)
Monocytes (Abs)	$10^3/mm^3$	>1.2 × ULN	18	4 (22.2)	17	3 (17.6)	27	7 (25.9)	62	14 (22.6)
Reticulocytes (Abs)	$10^3/mm^3$	<0.5 × LLN	11	5 (45.5)	11	6 (54.5)	13	2 (15.4)	35	13 (37.1)
		>1.5 × ULN	11	4 (36.4)	11	4 (36.4)	13	5 (38.5)	35	13 (37.1)

Source: Study A8851008 Clinical Study Report, adapted from Table 36. Hemoglobin and hematocrit values were not collected during the trial per protocol.

Clinical reviewer's comment: *It was difficult to assess any of the hematological laboratory test abnormalities as related to anidulafungin as the results could be explained by other factors such as underlying disease, comorbidities, and sepsis. There were no reports of serious drug-induced hematological adverse events such as hemolytic anemia or aplastic anemia.*

Renal Function

There were no clinically significant changes in postbaseline creatinine levels. Most subjects had normal creatinine at baseline and during the study. Six patients (9%) experienced changes in creatinine levels > ULN. The three patients with post baseline creatinine levels > 2x ULN had elevated creatinine levels at baseline. There were no reported cases of renal failure.

Table 10-11 A8851008: Maximum Post Baseline Shifts in Creatinine Level Categories

	Max. Creatinine Level Categories – Postbaseline, n/N (%)			Total Subjects N = 63 (100%)
Creatinine Categories at Baseline	**<=ULN**	**>ULN to <=2xULN**	**>2xULN**	
<=ULN	50 (79.4)	7 (11.1)	0	57 (90.5)
>ULN to <=2xULN	0	3 (4.8)	0	3 (4.8)

	Max. Creatinine Level Categories – Postbaseline, n/N (%)			Total Subjects N = 63 (100%)
Creatinine Categories at Baseline	<=ULN	>ULN to <=2xULN	>2xULN	
>2xULN	0	0	3 (4.8)	3 (4.8)

Source: ADLB dataset. J Review v. 13.1. The analysis included patients with creatinine values when a change from baseline value was not missing.

Clinical reviewer's comment: *Anidulafungin has negligible renal clearance; therefore, significant adverse renal effects are highly unlikely to be associated with the drug. Anidulafungin and other echinocandins are not recommended for treatment of fungal infections in the urinary tract because of the negligible amount of drug excreted in urine.*

Electrolytes

The most common electrolyte abnormality was a TEAE of hypokalemia observed in in 3 patients (4.5%) on anidulafungin therapy, Table 10-12. No age-dependent trends were observed for patients with serum chemistry abnormalities. No patients were discontinued from anidulafungin treatment because of abnormal electrolytes.

Table 10-12 A8851008: Creatinine, glucose, and electrolyte levels by age group – Safety Population

			1 Month to <2 Years (N=19)		2 to <5 Years (N=19)		5 to <18 Years (N=30)		Overall (N=68)	
Number of subjects evaluable			19 (100)		19 (100)		30 (100)		68 (100)	
Number (%) with laboratory abnormalities			19 (100)		18 (94.7)		30 (100)		67 (98.5)	
Group Parameter	Units	Criteria	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Renal function										
Blood urea nitrogen	mg/dL	>1.3 × ULN	7	2 (28.6)	9	3 (33.3)	12	4 (33.3)	28	9 (32.1)
Creatinine	mg/dL	>1.3 × ULN	19	0	18	2 (11.1)	30	5 (16.7)	67	7 (10.4)
Electrolytes										
Sodium	meq/L	<0.95 × LLN	19	0	18	0	30	4 (13.3)	67	4 (6.0)
		>1.05 × ULN	19	1 (5.3)	18	0	30	1 (3.3)	67	2 (3.0)
Potassium	meq/L	<0.9 × LLN	19	4 (21.1)	18	3 (16.7)	30	11 (36.7)	67	18 (26.9)
		>1.1 × ULN	19	2 (10.5)	18	1 (5.6)	30	3 (10.0)	67	6 (9.0)
Chloride	meq/L	<0.9 × LLN	17	0	18	1 (5.6)	26	3 (11.5)	61	4 (6.6)
		>1.1 × ULN	17	1 (5.9)	18	0	26	2 (7.7)	61	3 (4.9)
Bicarbonate (venous)	meq/L	<0.9 × LLN	18	2 (11.1)	15	6 (40.0)	26	7 (26.9)	59	15 (25.4)
		>1.1 × ULN	18	3 (16.7)	15	2 (13.3)	26	9 (34.6)	59	14 (23.7)
Calcium	meq/L	<0.9 × LLN	19	5 (26.3)	18	1 (5.6)	30	9 (30.0)	67	15 (22.4)
		>1.1 × ULN	19	0	18	0	30	1 (3.3)	67	1 (1.5)
Magnesium	mg/dL	>1.1 × ULN	19	2 (10.5)	17	0	29	4 (13.8)	65	6 (9.2)
		<0.9 × LLN	19	4 (21.1)	17	5 (29.4)	29	8 (27.6)	65	17 (26.2)
Clinical chemistry										
Glucose	mg/dL	<0.6 × LLN	19	0	18	2 (11.1)	29	2 (6.9)	66	4 (6.1)
		>1.5 × ULN	19	1 (5.3)	18	8 (44.4)	29	3 (10.3)	66	12 (18.2)

Source: Table 14.3.4.1.1.
Percentage for n was based on the N in that row.
Abbreviations: Abs=absolute; LLN=lower limit of normal; N=total number of subjects with normal or missing baseline with at least 1 observation of the given laboratory test while on study or during lag time; n=number of subjects with normal or missing baseline with a laboratory abnormality meeting specified criteria while on study; ULN=upper limit of normal.

In summary, no clinically significant changes were observed for any specific laboratory parameter. Observed laboratory test abnormalities were generally in line with those expected in a critically ill patient population with invasive candidiasis and multiple co-morbid diseases.

Clinical reviewer's comment: *A notable difference in the pediatric patients as compared to the adults in candidemia/invasive candidiasis trial, was the lower incidence of hypokalemia, 2.9% vs. 25% of patients, respectively; however, the reason for the difference is unclear.*

10.4.7. Vital Signs

A complete physical examination including vital signs (temperature, pulse, and blood pressure) was performed at screening. A targeted physical examination including vital signs was performed: on Days 3, 7, and 10; every 3 days from Day 11 through Day 34, unless in an outpatient setting where examinations were less frequent but not less than every 7 days (close monitoring of subjects treated in the outpatient setting was required); at EOIVT and EOT visits; and at the 2- and 6-week follow-up visits.

Clinically significant vital sign abnormalities and/or changes from baseline in vital signs were observed consistent with variations expected for a critically ill study population with sepsis due to *Candida* and were not suggestive of an effect by anidulafungin.

10.4.8. Electrocardiograms (ECGs)

No clinically significant abnormal electrocardiogram (ECG) findings were observed based on interpretations conducted at each study site.

10.4.9. QT

No cases of QTc prolongation *or torsade de pointes* were reported. A search for symptoms possible associated with QT prolongation yielded one TEAE of loss of consciousness of unknown causality at four days post treatment with anidulafungin. The adverse event was not associated with any specific ECG findings.

10.4.10. Immunogenicity

Not applicable to antifungal drugs.

10.5. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest

TEAEs of special interest known to be associated with the echinocandin class and described in the ERAXIS USPI, include hepatic adverse reactions, anaphylaxis/allergic reactions, infusion reactions, and convulsions. Most of the TEAEs were reported in the Investigations SOC (19%), Skin and Subcutaneous Tissue disorders SOC (15%) and Respiratory, Thoracic and Mediastinal disorders SOC (13%), see Table 10-13.

Table 10-13 A8851008: Treatment Emergent Adverse Events of Special Interest

TEAEs OF SPECIAL INTEREST	ANIDULAFUNGIN Total Subjects (N=68)
Any TEAE	**24 (35.3%)**
Eye disorders	**3 (4.4)**
Eyelid edema	1 (1.5)
Periorbital edema	2 (2.9)
General disorders and administration site conditions	**6 (8.8)**
Face edema	1 (1.5)
Generalized edema	2 (2.9)
Edema	1 (1.5)
Edema peripheral	2 (2.9)
Hepatobiliary disorders	**5 (7.4)**
Cholestasis	1 (1.5)
Hepatitis acute	1 (1.5)
Hepatomegaly	1 (1.5)
Hyperbilirubinemia	3 (4.4)
Ocular icterus	1 (1.5)
Infections and infestations	1 (1.5)
Liver abscess	1 (1.5)
Investigations	**13 (19.1)**
Alanine aminotransferase increased	7 (10.3)
Aspartate aminotransferase increased	5 (7.4)
Gamma-glutamyltransferase increased	2 (2.9)
Liver function test abnormal	1 (1.5)
Liver function test increased	1 (1.5)
Prothrombin time prolonged	1 (1.5)
Transaminases increased	4 (5.9)
Metabolism and nutrition disorders	1 (1.5)
Hypoalbuminemia	1 (1.5)
Nervous system disorders	**4 (5.9)**
Loss of consciousness	1 (1.5)
Seizure	3 (4.4)
Reproductive system and breast disorders	1 (1.5)
Penile edema	1 (1.5)
Scrotal edema	1 (1.5)
Respiratory, thoracic and mediastinal disorders	9 (13.2)
Acute respiratory failure	1 (1.5)
Bronchospasm	2 (2.9)
Cough	1 (1.5)
Dyspnea	1 (1.5)
Laryngospasm	1 (1.5)
Respiratory distress	2 (2.9)
Respiratory failure	1 (1.5)
Tachypnoea	1 (1.5)
Skin and subcutaneous tissue disorders	**10 (14.7)**
Erythema	2 (2.9)

TEAEs OF SPECIAL INTEREST	ANIDULAFUNGIN Total Subjects (N=68)
Hyperhidrosis	1 (1.5)
Pruritus generalized	1 (1.5)
Rash	6 (8.8)
Rash generalized	1 (1.5)
Urticaria	1 (1.5)
Vascular disorders	**5 (7.4)**
Hypotension	5 (7.4)
Shock	1 (1.5)

10.5.1. Hepatobiliary TEAEs

Search criteria using broad and narrow SMQs for hepatic AEs were used to identify hepatic TEAEs. Table 10-15 summarizes the hepatobiliary TEAEs experienced by 16 pediatric patients (23.5%). Hepatic TEAEs were reported across four SOCs, hepatobiliary disorders, infections and infestations, investigations, and metabolism and nutrition disorders. Patients experienced more than one hepatic TEAE and/or hepatic laboratory abnormality.

The hepatobiliary disorders SOC included 7 TEAEs reported in 5 patients which included acute hepatitis (1), hepatomegaly (1), hyperbilirubinemia (3), ocular icterus (1), and cholestasis (1). There were no cases of hepatic failure associated with anidulafungin or fluconazole.
Two of the 5 patients, Subject (b) (6) (F, 17y acute hepatitis) and Subject (b) (6) (M 3y, hepatomegaly) are discussed in section 10.4. Hyperbilirubinemia occurred in three patients; however, none met the criteria for Hy's Law. Total bilirubin levels resolved in one patient while hyperbilirubinemia was ongoing in two subjects who later died of sepsis/septic shock on Day 18 and Day 20, respectively. A 1-month-old white male experienced an episode of mild cholestasis assessed as unrelated to study drug. The subject received 9 days of anidulafungin, and the onset of the AE was 11 days post treatment on Day 20.

Among the 13 subjects with elevated aminotransferases reported as TEAEs, 11 patients (16.2%) developed increases in aminotransferases on anidulafungin treatment and two patients (2.9%) on fluconazole treatment.

Table 10-14 A8851008: Hepatobiliary Custom SMQ by SOC and Preferred Term

	Treatment with Anidulafungin by Age Groups			
Treatment Emergent Adverse Events	**< 2 years N = 19**	**2 to < 5 years N = 19**	**5 to < 18 years N = 30**	**N = 68**
Patients with a least one TEAEs	***4 (21%)***	***3 (15.8%)***	***9 (30%)***	***16 (23.5)***
Hepatobiliary Disorders	**1(5.3%)**	**1(5.3%)**	**3(10%)**	**5 (7.4%)**
Hepatitis acute	0	0	1	1
Ocular icterus	0	0	1	1
Cholestasis	1	0	0	1

	Treatment with Anidulafungin by Age Groups			
Treatment Emergent Adverse Events	**< 2 years N = 19**	**2 to < 5 years N = 19**	**5 to < 18 years N = 30**	**N = 68**
Hepatomegaly	0	1	0	1
Hyperbilirubinemia	0	1	2	3
Laboratory Investigations	**3 (15.8%)**	**3 (15.8%)**	**7 (23.3%)**	**13 (19.1%)**
Transaminases increased	1	0	3	4
ALT increased	2	2	3	7
AST increased	2	1	2	5
Liver function test incr.	0	1	0	1
Liver function abnormal	0	0	1	1
GGT increased	1	0	1	2
PT prolonged	0	1	0	1
Infections and Infestations				**1 (1.5%)**
Liver abscess	0	0	1	1
Metabolism and Nutrition				**1 (1.5%)**
Hypoalbuminemia	0	0	1	1

Source: Source: ADSL, ADAE, ADLB datasets. JMP Clinical v13.1 Includes data up to 30 days after last dose of study drug.

Anidulafungin was discontinued in three subjects [redacted] (b) (6) due to clinically significant elevations (5x to > 20x ULN) in aminotransferases with or without elevated total bilirubin levels:

Subject [redacted] (b) (6) was at 28-month-old female (Trisomy 21, heart failure) with candidemia and elevated transaminases at baseline. Multiple medications in the two-week period before the onset of transaminase elevations probably contributed to the abnormal baseline levels. Maximum elevations in ALT and AST levels of 1082 IU/L (24x ULN) and 840 IU/L (14x ULN), respectively, were reported on Day 4 of anidulafungin treatment. Anidulafungin was permanently discontinued and aminotransferases elevation resolved by Day 41. Total bilirubin was in the normal range throughout the study. There was a reasonable possibility that the sudden rise in aminotransferases was related to anidulafungin, see Table 10-15.

Table 10-15 Subject [redacted] (b) (6): ALT, AST and total bilirubin levels

Parameter (reference range)	Day 1	Day 3	Day 4	Day 5	Day 20	Day 41
ALT (5-45 IU/L)	174	430	1082	653	58 (range: 7-52 IU/L)	28 (range: 7-52 IU/L)
AST (20-60 IU/L)	222	395	840	244	65 (range: 15-39 IU/L)	39 (range: 15-39 IU/L)
Total bilirubin (0.2-1.2 mg/dL)	0.1	0.2	0.3	0.2	0.4	0.2

Source: Listing 16.2.8.1.1.
Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase.

Source: Study A8851008, Clinical Study Report

Subject [redacted] (b) (6), was a one-month-old male (congenital deformities) with candidemia who had elevated aminotransferases and total bilirubin levels at baseline. He developed further increases up to ALT 274 IU/L (6x ULN) and AST 281 IU/L (5x ULN) on anidulafungin at Day 14 (EOT visit). The baseline total bilirubin level [4.1 mg/dL (3x ULN) on Day 1] declined to the normal range while on anidulafungin. Alkaline phosphatase was < 2x ULN. Anidulafungin was discontinued on Day 14. ALT and AST levels declined off anidulafungin and were within normal ranges at follow up on Day 54. Table 10-16 summarizes the patient's hepatic enzyme levels throughout the study.

Table 10-16 Subject [redacted] (b) (6): ALT, AST and total bilirubin levels

Test Date (Day)	Laboratory Test			
	Alanine Aminotransferase (reference range: 13 to 45 IU/L)	Aspartate Aminotransferase (reference range: 15 to 60 IU/L)	Alkaline Phosphatase (reference range: 150 to 420 IU/L)	Total Bilirubin (reference range: 0 to 1.2 mg/dL)
[redacted] (b) (6) (Day 1)	143	117	358	4.1
[redacted] (Day 3)	114	100	311	3.2
[redacted] (Day 7)	107	117	300	2.6
End of Treatment Visit; [redacted] (b) (6) (Day 14)	274	281	523	1.6
Follow-up 1 Visit; 06 [redacted] (b) (6) Day 26)	57	52	391	0.6
[redacted] (Day 47)	68	90	285	0.5
Follow-up 2 Visit; 03 [redacted] (b) (6) (Day 54)	41	55	351	Not provided

Source: Study A8851008, Clinical Study Report

The third patient, Subject [redacted] (b) (6), a 5-year-old male, is described in the next section under severe hepatic TEAEs.

Severe hepatic TEAEs

Three patients (4.4%) experienced severe hepatic AEs. Two of the three patients died; however, the hepatic TEAEs were not directly related to their deaths.

Subject [redacted] (b) (6), a 5-year-old male (medulloblastoma, candidemia) had normal baseline levels of ALT, AST, total bilirubin, and alkaline phosphatase. He experienced an SAE of a sudden severe elevation in ALT 1887 IU/L (46x ULN) and AST 2329 IU/L (61x ULN) with a normal bilirubin on Day 10 which resulted in discontinuation of anidulafungin on the same day (Table 10-17). ALT and AST remained elevated at the time of the patient's death due to progression of medulloblastoma on Day 12. An association with anidulafungin and the sudden severe increase in aminotransferase levels cannot be ruled out.

Table 10-17 Subject (b) (6): ALT, AST and total bilirubin levels

Parameter (reference range)	Day 1	Day 3	Day 5	Day 7	Day 10
ALT (0-41 IU/L)	7.4	15	12.9	21.4	1887
AST (0-38 IU/L)	11	20	13	23	2329
Total bilirubin (0.2-1 mg/dL)	0.25	0.17	NA	0.16	0.58

Source: Listing 16.2.8.1.1.
Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; NA=not available.

Source: Study A8851008, Clinical Study Report

Clinical reviewer's comment: *There was a reasonable possibility that the severe rise in hepatic transaminases was related to anidulafungin. However, factors that could have contributed to the elevated transaminases prior to the patient's death included progression of underlying malignancy and polypharmacy with multiple concomitant medications many of which are associated with hepatoxicity such as diazepam, ketamine, omeprazole, glucagon, ondansetron, fentanyl, midazolam, metamizole sodium, cefuroxime, paracetamol, lorazepam, and methadone.*

Subject (b) (6), a 7-year-old male (Cushing's Syndrome, dermatomyositis, candidemia) experienced mildly elevated ALT, ocular icterus (Day 12), and severe hyperbilirubinemia (total bilirubin 13.9 mg/dL) on Day 14, see Table 10-18. The patient had a history of hepatic impairment and hepatomegaly for two years prior to study enrollment. He received one dose of anidulafungin before it was discontinued due to generalized pruritus on Day 1. He also developed acute pancreatitis on Day 12. All TEAEs except generalized pruritus were considered by the investigator as unrelated to anidulafungin and they remained elevated until the patient's death due to septic shock on Day 20.

Table 10-18 Subject (b) (6): ALT, AST and total bilirubin levels

Test Date (Day)	Laboratory Test				
	ALT (reference range: 7 to 40 IU/L)	AST (reference range: 13 to 40 IU/L)	Alkaline phosphatase (reference range: 116 to 515 IU/L)	Albumin (reference range: 2.8 to 5.4 g/dL)	Total bilirubin (reference range: 0-1.3 mg/dL)
(b) (6) (Day 1)	45	16	27	2.94	0.9
EOT visit; (b) (6) (Day 2)	63	37	34	2.79	1.1
Follow-up 1; (b) (6) (Day 14)	92	119	40	1.8	13.9

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; EOT = end of treatment

Source: Study A8851008, Clinical Study Report

Subject (b) (6), a 20-month-old male with candidemia, had elevated ALT/AST levels at baseline. He had a moderately elevated GGT on Day 3 and developed increases in ALT 666 IU/L (12x ULN) and AST 664 IU/L (11 x ULN) on Day 7 of anidulafungin treatment, see Table 10-19. Total bilirubin and alkaline phosphatase remained within the normal range throughout the study. Treatment with anidulafungin was continued which was a protocol violation. Hepatic TEAEs were probably associated with anidulafungin and with chemotherapeutic drugs, vincristine and daunorubicin, administered on Day -1 prior to treatment with anidulafungin. ALT and AST levels began to decline around Day 11 and were within the normal range at follow-up on Day 57.

Table 10-19 Subject (b) (6): ALT, AST and total bilirubin levels

Parameter (reference range)	Day 1	Day 3	Day 5	Day 7	Day 11	Day 14	Day 16	Day 28	Day 57
ALT (16-57 IU/L)	183	193	177	666	224	133	106	81	46
AST (15-59 IU/L)	113	82	96	664	56	73	61	40	36
Total bilirubin (0.1-1.2 mg/dL)	0.8	1.1	0.9	0.7	1.2	0.7	0.9	0.5	0.3

Source: Listing 16.2.8.1.1.
Note: total bilirubin values were rounded from source to accommodate the in-text table; refer to Listing 16.2.8.1.1 for raw values.
Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase.

Source: Study A8851008, Clinical Study Report

Clinical reviewer's comment: *Hepatobiliary TEAEs including hepatic laboratory abnormalities were more common in the 5 to 17-year-old age group (30%) as compared to younger pediatric age groups, 2 to 5y (15%) and < 2 years (21%). A definitive assessment of any age-related hepatic adverse events was not possible due to the small numbers of patients in each age group and the heterogeneity of co-morbid diseases and concomitant medications.*
The frequency of any hepatobiliary TEAEs was slightly lower among pediatric patients (23.5%) as compared to adults (24.4%) with candidemia/invasive candidiasis in the VER002-9 trial, see Table 10-20 submitted by the applicant on 8.28.2020. Elevated aminotransferases including hepatic enzymes reported as TEAEs were slightly higher in the pediatric study (18 adverse events) compared to adult study (14 events), Table 10-20. In the VER002-9 study report, submitted in the NDA on 11.22.2019, there is small discrepancy in that 16 adverse events of elevated aminotransferases including elevated hepatic enzymes were reported as TEAEs in Table 48 of the study report.

Table 10-20. Study VER002-9: Incidence of Treatment-Emergent Hepatobiliary Adverse Events - Intent-to-Treat Population

Anidulafungin Protocol scsa8850080a
Incidence of Treatment-Emergent Adverse Events by Adverse Events of Special Interest (Hepatobiliary Events)
Intent-to-Treat Population

System Organ Class Prefferred term	Anidulafungin (N=131)	Fluconazole (N=125)	Total (N=256)
Patients with any AE	32 (24.4%)	36 (28.8%)	68 (26.6%)
Gastrointestinal disorders	3 (2.3%)	6 (4.8%)	9 (3.5%)
Ascites	3 (2.3%)	6 (4.8%)	9 (3.5%)
Hepatobiliary disorders	3 (2.3%)	3 (2.4%)	6 (2.3%)
Cholestasis	1 (0.8%)	1 (0.8%)	2 (0.8%)
Hepatic pain	0	1 (0.8%)	1 (0.4%)
Hepatomegaly	1 (0.8%)	0	1 (0.4%)
Hyperbilirubinaemia	0	1 (0.8%)	1 (0.4%)
Jaundice	1 (0.8%)	0	1 (0.4%)
Infections and infestations	0	2 (1.6%)	2 (0.8%)
Hepatic candidiasis	0	1 (0.8%)	1 (0.4%)
Hepatitis C	0	1 (0.8%)	1 (0.4%)
Investigations	28 (21.4%)	30 (24.0%)	58 (22.7%)
Alanine aminotransferase abnormal	1 (0.8%)	0	1 (0.4%)
Alanine aminotransferase increased	5 (3.8%)	6 (4.8%)	11 (4.3%)
Aspartate aminotransferase increased	2 (1.5%)	8 (6.4%)	10 (3.9%)
Blood alkaline phosphatase abnormal	1 (0.8%)	0	1 (0.4%)
Blood alkaline phosphatase increased	14 (10.7%)	13 (10.4%)	27 (10.5%)
Blood bilirubin increased	4 (3.1%)	2 (1.6%)	6 (2.3%)
Hepatic enzyme abnormal	0	1 (0.8%)	1 (0.4%)
Hepatic enzyme increased	6 (4.6%)	13 (10.4%)	19 (7.4%)
Metabolism and nutrition disorders	3 (2.3%)	4 (3.2%)	7 (2.7%)
Hypoalbuminaemia	3 (2.3%)	4 (3.2%)	7 (2.7%)
Nervous system disorders	0	1 (0.8%)	1 (0.4%)
Hepatic encephalopathy	0	1 (0.8%)	1 (0.4%)

AE terms included in search criteria: BILIRUBINURIA, CHOLESTATIS OF PREGNANCY, JAUNDICE ACHOLURIC, JAUNDICE EXTRAHEPATIC OBSTRUCTIVE, LIVER TRANSPLANT REJECTION
SMQ categories included in search criteria: Cholestasis and jaundice of hepatic origin; Hepatitis, non-infectious; Liver infections; Liver related investigations, signs and symptoms; Liver-related coagulation and bleeding disturbances; Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
Subjects are counted only once in each row.
Studies included VER002-9.
PFIZER CONFIDENTIAL SDTM Creation: . (.)Table Generation: 25AUG2020 (17:08)
' Output File: ./CSR_ICON/scsa8850080a/hepa

Source: Table 1 in Applicant's submission, dated 08.28.2020, to NDA 21-632.

The common co-morbid diseases in the pediatric and adult trials were different. In adults, comorbid diseases included endocrine/metabolic disorders such as diabetes mellitus (~50%), bacterial sepsis and recent surgical history (~40% each), neoplastic diseases (~20%), and solid organ transplants (5%). Most adults in VER002-9 were not neutropenic whereas in the pediatric study, blood and lymphatic disorders such as anemias (non-hemolytic), neutropenia and other cytopenias related to bone marrow depression occurred in ~45% of patients. Other co-morbid diseases included congenital, familial and genetic disorders related to several body organ systems (~34%), bacterial and viral infections (~25%), and traumatic injuries (~11%).

10.5.2. Hypersensitivity/ Infusion Reactions

Search criteria for TEAEs (using broad and narrow SMQs) associated with anaphylaxis, were used to identify possible anaphylactic, allergic reactions, or infusion-related reactions associated with anidulafungin. No cases of anaphylaxis or anaphylactoid reactions were reported for anidulafungin. One TEAE of facial edema indicative of an anaphylactic reaction was associated with fluconazole.

Histamine-mediated infusion reactions are known to be associated with anidulafungin. In this study, adverse reactions occurring during infusion or within 1-hour post infusion of anidulafungin were identified in 5 (7.4%) patients and included skin erythema, periorbital edema, and generalized pruritus, Table 10-21. Most of these TEAEs were mild. One patient developed generalized pruritus after the first infusion which led to the discontinuation of anidulafungin on Day 1.

Periorbital edema (mild) was reported in two 4-year-old patients at the same site in Brazil. One of the patients developed periorbital edema 10 minutes following the end of anidulafungin infusion on Day 19 of treatment. The other patient developed periorbital edema on Day 3 of anidulafungin treatment, but it was not reported if it was infusion-related. In both cases, the periorbital edema resolved quickly, and no treatment was administered.

A review of the other TEAEs indicated no relationship to anidulafungin, for example, laryngospasm occurred at 18 days post treatment with anidulafungin and was related to laryngotracheobronchitis. Hypotension and shock were associated with septic shock and TEAEs of respiratory distress, respiratory failure, and bronchospasm (at 35 days post anidulafungin treatment) were associated with underlying pulmonary disease. An episode of “red man syndrome” was reported as a TEAE for one male patient with candidemia; however, this AE occurred prior to study entry and could not have been associated with anidulafungin.

Infusion rates were not at the protocol-specified rate of 1.1 mg/min (protocol violations) in 20 patients and they exceeded 1.1 mg/min in 9 of the patients. An infusion rate not exceeding 1.1 mg/min is recommended in the current USPI to reduce the frequency of infusion reactions; see section 6.2.1.

Table 10-21 Study A8851008: Treatment Emergent Adverse Events Associated with Hypersensitivity - Safety Population

	Treatment with Anidulafungin by Age Group			
Treatment Emergent Adverse Events of Special Interest	**1 month to <2 n = 19**	**2 - <5y n = 19**	**5 - <18y n = 30**	**Totals N = 68**
Anaphylaxis SMQ - No. of subjects with at least 1 TEAE	**6 (31.6%)**	**6 (31.6%)**	**3 (10.0%)**	**15 (22.1%)**
Hypotension	0	1 (5.3%)	1 (3.3%)	2 (2.9%)
Edema	0	0	1 (3.3%)	1 (1.5%)
Rash*	3 (15.8%)	1 (5.3%)	2 (6.6%)	6 (8.8%)

	Treatment with Anidulafungin by Age Group			
Treatment Emergent Adverse Events of Special Interest	**1 month to <2 n = 19**	**2 - <5y n = 19**	**5 - <18y n = 30**	**Totals N = 68**
Pruritus	0	1(5.3%)	0	1 (1.5%)
Bronchospasm	0	0	1 (3.3%)	1 (1.5%)
Laryngospasm	1 (5.3%)	0	0	1 (1.5%)
Eyelid edema	1 (5.3%)	0	0	1 (1.5%)
Erythema	1 (5.3%)	0	0	1 (1.5%)
Periorbital edema	0	2 (10.5%)	0	2 (2.9%)
Cough	0	1 (5.3%)	0	1 (1.5%)
Respiratory distress	0	1 (5.3%)	0	1 (1.5%)
Respiratory failure	0	1 (5.3%)	0	1 (1.5%)
Shock	0	1 (5.3%)	0	1 (1.5%)

Source: ADAESPI dataset.
**Rash includes preferred terms such as rash and rash generalized.*

Clinical reviewer's comment: *Given the close temporal association with anidulafungin infusion, the TEAEs of skin erythema, periorbital edema, and generalized pruritus were attributed to anidulafungin in pediatric patients. It is not clear if the recommended infusion rate of anidulafungin was exceeded in these patients. In the adult trial (VER002-9), dyspnea (6.9%) and flushing (2.3%) were reported as infusion-related adverse events.*
Pruritus, rash, and facial edema were reported as hypersensitivity reactions in adults. Hypersensitivity reactions such as angioneurotic edema, erythema, pruritus, and urticaria are listed as occurring in <2% of adult patients in the Adverse Reactions section of the ERAXIS USPI. Anaphylactic shock, anaphylactic reaction, and bronchospasm are listed in the Postmarketing Experience section. No additional labeling changes are required regarding hypersensitivity or infusion reactions.

10.5.3. Skin Rashes

Skin rashes occurred in 6 subjects (8.8%) and were reported as mild or moderate in severity and were non-serious adverse events. It was not reported if any of the rashes were infusion-related.

Two case reports are noteworthy, a TEAE of "toxic skin eruption" or "toxic dermatosis" and one case of urticaria, summarized in Table 10-22. A TEAE of "toxic skin eruption" was reported in a 20-month-old patient on the final day (Day 16) of anidulafungin treatment; no further details on the rash were provided in the case narrative. The investigator was unable to distinguish which medication caused the TEAE as the patient was on multiple concomitant medications including chemotherapy. One case of mild urticaria occurred in a 3-year-old male on Day 3 of treatment and it had resolved within 24 hours after a single dose of IV anti-histamine. Morphine was the suspect drug in this instance. These two cases increase the total of patients with skin disorders to 8 patients (11%). Anidulafungin was continued without dose adjustments in all patients. No symptoms of anaphylaxis such as breathing difficulty, angioedema, hypotension, or shock were reported with skin rashes. There were no reports of life-

threatening adverse reactions such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

Table 10-22 A8851008: Selected cases with skin rash

TEAE	Subject/ sex/age	Duration of TEAE	Anidulafungin Treatment	Con. Meds	Tx for TEAE	D/C study drug	Recovered
Toxic skin eruption	(b) (6) M/ 20 months	Day 16 to 20	Day 1 thru 16	Y	None	No	Y
Urticaria (mild)	(b) (6) M/3y	Day 3 to 4	Day 1 to 13	Y	IV anti-histamine	No	Y

Source: ADAESPI dataset; Y=Yes; Con: Concomitant; Meds: Medications; Tx: Treatment; D/C: Discontinued

Clinical reviewer's comments: *All subjects were on anidulafungin treatment at the onset of rash; therefore, an association with the study drug cannot be ruled out. Skin rashes were more common in pediatric patients than in adults with invasive candidiasis, i.e., 9% of patients in this pediatric study A8851008 and 3% of patients in the adult trial, VER002-9. Urticaria occurred at similar rates (~1.5%) in pediatric and adult patients. There were no cases of SJS or TEN in the pediatric or adult studies.*

10.5.4. Catheter IV /Device Related Adverse Events

Eight subjects (11.8%) experienced catheter site AEs such as erythema, hematoma or hemorrhage, inflammation, pain, or rash at the IV catheter site. Most of the AEs occurred in the 5 to < 18 years old age group than in the younger two age groups. All the catheter-site TEAEs resolved within 24 hours except for one TEAE of "catheter site pain" which took 6 days to resolve.

10.5.5. Seizure

Three subjects (4.4%) experienced seizures, a four-year-old female, and 16-year-old male and a 22-month-old female, on Day 7, Day 12 and Day 5, respectively. All the patients had a prior history of seizure disorder and all were receiving concomitant antiepileptic drugs. Anidulafungin could have exacerbated seizures as they occurred while patients were on anidulafungin treatment and thus an association with study drug cannot be ruled out. Seizure is listed in the adverse reactions section of the current ERAXIS USPI.

10.5.6. Hypoglycemia

Hypoglycemia was reported in 4 (6%) patients receiving anidulafungin, 2 subjects in the 2 to 5y age group and 1 patient each in the other two age groups. An unspecified treatment for hypoglycemia was administered to 2 patients. None of the events were categorized as SAEs. Hypoglycemia was categorized as severe in a 4-year-old female with a history of hypoglycemia and the SAE resolved without sequelae; however, this SAE occurred 22 days after the last dose of anidulafungin treatment and was unrelated to anidulafungin. The dose of anidulafungin was

not changed in any patient. The investigator considered one mild case of hypoglycemia possibly related to anidulafungin. Hypoglycemia is listed as an adverse reaction in the current ERAXIS USPI.

10.5.7. Anesthetic exacerbation of infusion related reactions

Anesthetic exacerbation of infusion-related reactions associated with anidulafungin is a potential risk.[24, 25, 26] Rats given high doses of anidulafungin experienced a worsening of allergic reactions related to infusion with anidulafungin and anesthesia. The cause of the worsening of these reactions in rats is unknown. Although the relevance of this finding to humans is unknown, any patient experiencing allergic reaction related to infusion and receiving concurrent anesthesia might be at risk based on the nonclinical safety signal. To be identified as a suspect case in study A8851008, the AE had to occur during the anidulafungin infusion or within 60 minutes following completion of the anidulafungin infusion and there also had to be anesthetic administration within 60 minutes of infusion. One patient had anesthesia for a cholecystectomy during the trial and there were no reported events suggestive of anesthetic exacerbation of infusion-related reactions.

10.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

10.7. Safety Analyses by Demographic Subgroups

There were 38 male and 30 female patients in the pediatric trial. TEAEs occurring in ≥ 3 patients are summarized by sex in Table 10-23. Vomiting and diarrhea were common in both sexes; however, these TEAEs were almost twice as common in females (~30%) as compared to male patients (~ 16%). Elevations in hepatic aminotransferases were more common in males (10%) as compared to female patients (3%), however, the small numbers of patients impede any definitive conclusion about sex-related differences in TEAEs.

An analysis of TEAEs by race is not shown because there was a large imbalance in the distribution of races in the study, i.e., Caucasian (79.4%), Black or African American (1.5%), Asian (8.8%), Other (10.3%); therefore, a comparison of TEAEs across race categories would be uninformative. An analysis of TEAEs by country or study site is not shown because the analysis across sites was uninformative due to the small number of patients enrolled at all but 2 of the 27 study sites.

[24] https://laegemiddelstyrelsen.dk/upload/rmp/28105878016%2014-11-2018.pdf
[25] https://www.ema.europa.eu/en/documents/scientific-discussion/ecalta-epar-scientific-discussion_en.pdf
[26] https://www.medicines.org.uk/emc/product/10698/smpc#gref

Table 10-23 A8851008: TEAEs by sex and occurring in ≥ 3 subjects (4%) – Safety Population

Treatment Emergent Adverse Event	F (N=30)	M (N=38)	Total (N=68)
Vomiting	10 (33.3)	6 (15.8)	16 (23.5)
Diarrhea	9 (30.0)	6 (15.8)	15 (22.1)
Pyrexia	6 (20.0)	7 (18.4)	13 (19.1)
Anemia	5 (16.7)	4 (10.5)	9 (13.2)
Epistaxis	6 (20.0)	3 (7.9)	9 (13.2)
Alanine aminotransferase increased	1 (3.3)	6 (15.8)	7 (10.3)
Headache	3 (10.0)	4 (10.5)	7 (10.3)
Abdominal pain	1 (3.3)	5 (13.2)	6 (8.8)
Rash	3 (10.0)	3 (7.9)	6 (8.8)
Aspartate aminotransferase increased	1 (3.3)	4 (10.5)	5 (7.4)
Febrile neutropenia	3 (10.0)	2 (5.3)	5 (7.4)
Hypotension	2 (6.7)	3 (7.9)	5 (7.4)
Pneumonia	2 (6.7)	3 (7.9)	5 (7.4)
Thrombocytopenia	1 (3.3)	4 (10.5)	5 (7.4)
Abdominal distension	2 (6.7)	2 (5.3)	4 (5.9)
Agitation	1 (3.3)	3 (7.9)	4 (5.9)
Hypocalcemia	0	4 (10.5)	4 (5.9)
Hypoglycemia	1 (3.3)	3 (7.9)	4 (5.9)
Hyponatremia	2 (6.7)	2 (5.3)	4 (5.9)
Nausea	1 (3.3)	3 (7.9)	4 (5.9)
Neutropenia	2 (6.7)	2 (5.3)	4 (5.9)
Staphylococcal bacteremia	3 (10.0)	1 (2.6)	4 (5.9)
Transaminases increased	1 (3.3)	3 (7.9)	4 (5.9)
Upper respiratory tract infection	1 (3.3)	3 (7.9)	4 (5.9)
Bacteremia	0	3 (7.9)	3 (4.4)
Device related infection	1 (3.3)	2 (5.3)	3 (4.4)
Hyperbilirubinemia	0	3 (7.9)	3 (4.4)
Hypoproteinemia	2 (6.7)	1 (2.6)	3 (4.4)
Leukopenia	2 (6.7)	1 (2.6)	3 (4.4)
Lower respiratory tract infection	1 (3.3)	2 (5.3)	3 (4.4)
Pancytopenia	2 (6.7)	1 (2.6)	3 (4.4)
Seizure	2 (6.7)	1 (2.6)	3 (4.4)
Sepsis	2 (6.7)	1 (2.6)	3 (4.4)
Septic shock	1 (3.3)	2 (5.3)	3 (4.4)
Thrombocytosis	0	3 (7.9)	3 (4.4)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
TEAE - Dataset: Adverse Events; Filter: TRTEMFL = 'Y'; Percent Threshold: >= 5%.

10.8. Specific Safety Studies/Clinical Trials

Not applicable.

10.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

Human Reproduction and Pregnancy

Not applicable.

Pediatrics and Assessment of Effects on Growth

Not applicable. Anidulafungin IV is intended for short term use. Effects on growth patterns in pediatric patients were not assessed.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable to antifungal drugs.

10.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Other sources of safety data for anidulafungin include two small pediatric safety/ PK studies, information from Pfizer's global safety database, and review of published literature:

Safety/PK Studies
Study VER001, the Duke University Investigator Initiated Research Study (Duke IIR Study), was a multicenter, open-label, safety/ PK study of anidulafungin conducted in infants and neonates.[27] A total of 15 patients (8 neonates, 7 infants) with ages ranging from 2 to 451 days were enrolled and stratified by estimated gestational age (EGA) in two main categories: ≤ 120 days of age or 4 - 24 months. Most patients (53%) were critically ill on mechanical ventilation at the start of the study and 2 (13%) were supported by ECMO. Patients received daily infusions of anidulafungin 1.5 mg/ kg for an average of five days.

Safety Summary: There were two deaths not related to study drug, one in each age group. Three subjects (20%) experienced five SAEs which included 2 deaths, and 1 neonate experienced oliguria, hypotension, and an abnormal KUB (kidneys, ureters, bladder) radiograph. Deaths were related to complications of a hypoplastic left heart syndrome (n=1) and discontinuation of ECMO support (n=1). None of the SAEs were attributed to anidulafungin. The most common TEAE was worsening hyperbilirubinemia, Table 10-24. Four patients experienced hepatobiliary adverse events: two subjects with hepatic enzymes (≤3x ULN) and the two subjects with hyperbilirubinemia; both patients had episodes of direct

[27] Cohen-Wolkowiez, M, DK Benjamin DK Jr, Piper L, et al. Safety and Pharmacokinetics of Multiple-Dose Anidulafungin in Infants and Neonates. Clin Pharmacol Ther. 2011 May;89(5):702-7. doi: 10.1038/clpt.2011.26.

hyperbilirubinemia prior to starting anidulafungin. The AEs of hyperbilirubinemia led to discontinuation of anidulafungin and resolved off study drug. Overall, there was no discernible pattern of toxicity or differences between the age groups regarding TEAEs, SAEs or degree of severity of AEs in this small study.

Clinical reviewer's comment: *There were no new adverse events for anidulafungin reported in study VER-001.*

Pharmacokinetic data from a PK/ safety pediatric study (NCT000068471) are published and described in the Clinical Pharmacology section (12.3) in the current ERAXIS USPI. This was a multicenter, open label, sequential dose-escalation study from 0.75 mg/kg/day to 1.5 mg/kg/day to assess the safety and PK profile of anidulafungin in 24 immunocompromised children, 2 to 17 years of age, with neutropenia.[28] There were two deaths unrelated to study drug. The most common AE, experienced by 11 (44%) patients, was pyrexia. Other common AEs experienced by 5 (21%) patients were mucosal inflammation, graft-versus-host disease (GVHD), and vomiting (6 [24.0%] patients each) and cough, hypertension, and hypomagnesemia (5 [20%] patients each). One patient developed a grand mal seizure which led to discontinuation of anidulafungin. Five patients (21%) experienced hepatobiliary AEs, all of which were elevations (< 3x ULN) of hepatic enzymes (ALT, AST, ALKP, total bilirubin). No patients fulfilled the criteria for Hy's Law. There was no dose-response relationship between the 0.75 mg/kg and the 1.5 mg/kg dosage and deaths, SAEs, or TEAEs.

Clinical reviewer's comment: *The AES associated with anidulafungin in this study are consistent with TEAEs reported in study A8851008 and with post market safety reports. No new AEs were identified for anidulafungin.*

Applicant's Global Safety Database

The applicant provided a summary of postmarket safety for anidulafungin from their global safety database. They estimate that 801,962 patients were exposed to anidulafungin worldwide since the drug was first approved through October 15, 2018; 186,768 patients were exposed to anidulafungin in the USA during the same time frame.

A total of 1127 cases (1,638 AEs) were received from spontaneous sources in 16 countries. Among the total postmarket cases, 32 cases (56 AEs) representing 2.8% of total postmarket cases involved pediatric patients. The AEs reported more than once included product use issue (10), pyrexia (5), drug administered to patient of inappropriate age, off-label use and respiratory disorder (3 each), anaphylactic shock, drug ineffective, metabolic acidosis, rash and transaminases increased (2 each). The two cases of elevated hepatic enzymes occurred in neonates (0 to 27 days old). No new adverse reactions related to ERAXIS were identified by the

[28] Benjamin DK, Driscoll T, Seibel NL, et al. Safety and pharmacokinetics of intravenous anidulafungin in children with neutropenia at high risk for invasive fungal infections. Antimicrob Agents Chemother 2006;50(2):632-8.

Applicant.

Published Literature

A review of published literature was conducted by the reviewer for novel adverse reactions associated with anidulafungin. The search revealed one case-report of flash pulmonary edema occurring near the end of an anidulafungin infusion.[29] A 52-year-old male with multiple myeloma, fever, and neutropenia had an acute onset of spasmodic cough with shortness of breath, chest tightness, and oxygen saturation of 88%, with subsequent new bilateral perihilar and interstitial edema seen on chest x-ray. A baseline chest x-ray was negative for these findings. Concomitant medications on the day of anidulafungin administration included acyclovir, meropenem, vancomycin and acetaminophen. The patient was treated with diphenhydramine, hydrocortisone, and albuterol with complete recovery within a few hours, and he a normal chest X-ray the following day. A cardiogenic etiology was not found. Given the temporal association with infusion of anidulafungin, it is highly likely that anidulafungin was the cause of the episode of flash pulmonary edema.

Clinical reviewer's comment: *No additional cases of flash pulmonary edema were found in the reviewer's search of the medical literature search since this first case report in 2012. No cases were reported with the other echinocandins in clinical use, caspofungin and micafungin. It is unlikely that this was a case of systemic capillary leak syndrome as the patient did not experience shock and massive edema, and he recovered quickly. It is unclear if there was any safety signal in animal studies as pulmonary edema associated with anidulafungin treatment was reported in one study of neutropenic rabbits with experimental pulmonary aspergillosis.*[30]

10.11. Integrated Assessment of Safety

Data from 68 patients in study A8851008 provides the foundation for the safety assessment of anidulafungin in pediatric patients, one month to 17 years of age. Supplemental safety information in an additional 39 patients came from two small pediatric safety/PK studies, VER001 (n= 15) and VER002-12 (n = 24) which makes a total of 117 pediatric patients 0 to 17 years of age exposed to anidulafungin. There were no major differences in the types of TEAEs reported in study A8851008 and in the other two pediatric studies.

The major limitation of the pediatric safety data is the lack of comparative safety in all three studies; therefore, the attribution of any AE to anidulafungin was challenging.

[29] Hindahl CB and Wilson JW. Flash pulmonary oedema during anidulafungin administration. Journal of Clinical Pharmacy and Therapeutics, 2012, 37, 491–493.
[30] Petraitis V, Petraitiene R, Groll AH et al. Antifungal efficacy, safety, and single-dose pharmacokinetics of LY303366, a novel echinocandin B, in experimental pulmonary aspergillosis in persistently neutropenic rabbits. Antimicrob Agents Chemother, 1998; 42:2898–2905.

The pediatric deaths were associated with invasive candidiasis or other complications related to the patients' underlying diseases, i.e., bacteremia/septic shock, respiratory or multiorgan failure, intracranial hemorrhage, or progression of underlying malignancy.

Gastrointestinal disorders such as vomiting and diarrhea were the most common adverse reactions associated with anidulafungin in pediatric patients, with similar incidence rates to adults in the invasive candidiasis/candidemia trial, VER002-9.

Hepatobiliary disorders, mostly elevated aminotransferases, were the most commonly observed laboratory abnormalities associated with anidulafungin. Many of the patients had elevated aminotransferases and total bilirubin at baseline; however, and it is possible that anidulafungin contributed to postbaseline increases in these laboratory tests. Anidulafungin was discontinued in 4% of subjects due to clinically significant elevations in ALT with or without elevated total bilirubin levels. Hyperbilirubinemia occurred in 4% of patients; however, none met the criteria for Hy's Law. Hepatobiliary laboratory abnormalities returned to normal range or to baseline values in most patients except for one patient who died of progression of the medulloblastoma and had severely elevated ALT and AST levels at the time of death and two patients with hyperbilirubinemia who died of sepsis/septic shock.

Other less common adverse reactions were skin rashes and infusion-related reactions. Anidulafungin was continued in all patients who developed a skin rash (rash, toxic dermatosis, urticaria) and the patients improved on while on anidulafungin therapy suggesting that at least some of the rashes were unlikely to be related to anidulafungin.

Echinocandins have been associated with histamine-mediated infusion reactions in adults and pediatric patients in published literature. Infusion-related reactions were manifested as skin erythema, periorbital edema, generalized pruritus in pediatric patients.

Vomiting, diarrhea, generalized pruritus, and increased transaminases were considered treatment-related and led to the discontinuation of anidulafungin.

Overall, anidulafungin was generally well tolerated. Most TEAEs were mild or moderate in severity and were assessed as unrelated to anidulafungin and most of these adverse events resolved during the study period.

Adverse reactions in the pediatric study A8851008 were compared to those reported in the adult candidemia/invasive candidiasis trial, VER002-9. Vomiting and diarrhea were the most common adverse reactions associated with anidulafungin in pediatric and adult patients. The frequency of any hepatobiliary TEAE were slightly lower among pediatric patients as compared to adults with candidemia/invasive candidiasis in the VER002-9 trial. Elevated hepatic aminotransferases reported as TEAEs and appeared at a slightly higher frequency in pediatric patients than was observed in adult patients with candidemia and other forms of invasive

candidiasis trial in the phase 3, VER002-9. Differences in severity of invasive candidiasis and co-morbid diseases between the two populations or chance may have contributed to the observed differences. Other differences in adverse reactions in the two populations were more skin rashes in pediatric patients and more hypokalemia in adults.

The published literature reports hepatobiliary adverse reactions associated with anidulafungin and the echinocandin class of antifungal drugs; however, progression to serious hepatic injury and hepatic failure is uncommon.[31] Anidulafungin was shown to be well tolerated by adults with decompensated liver disease, multiorgan failure, and high-risk liver transplant with proven or probable invasive fungal disease.[32] Uniquely among the FDA-approved echinocandins, anidulafungin is eliminated almost exclusively by slow chemical degradation. It is metabolized in the liver but not by the P450 system. Dose adjustments are not required in mild, moderate or severe hepatic insufficiency. Hepatotoxicity has been consistently reported for all classes of antifungal drugs, polyenes, triazoles, and echinocandins and most of the available hepatic safety data is from adults with limited data in pediatric patients. Based on the available data, antifungal triazoles have the highest relative potential for hepatotoxicity, followed by terbinafine, amphotericin B products, and the echinocandins.[31] A search of published literature reports did not identify any new adverse reactions except for an isolated case report of flash pulmonary edema in an adult following administration of anidulafungin.[29]

Treating neonates with candidemia/ invasive candidiasis requires consideration of higher doses of anidulafungin for adequate coverage of disseminated candidiasis and *Candida* meningoencephalitis. A dose of anidulafungin that adequately penetrates the CNS and ocular tissue has not been established but will be higher than the approved dose based on nonclinical studies. Higher doses of anidulafungin would result in higher doses of the formulation excipient polysorbate 80 which has been associated with potentially life-threatening toxicity including hepatotoxicity in low-birth weight infants.[33] The authors reported a fatal syndrome characterized by progressive clinical deterioration with unexplained thrombocytopenia, renal dysfunction, cholestasis, and ascites in 8 infants who had received E-Ferol, an intravenous vitamin E supplement; they proposed that the likely cause of the observed toxicities was polysorbate. The data on polysorbate toxicity are limited, and the only other reports were a single case report of cardiogenic shock in an infant who received an overdose of intravenous

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[31] Palazzi DL, Arrieta A, Castagnola E, et al. Candida speciation, antifungal treatment and adverse events in pediatric invasive candidiasis: results from 441 infections in a prospective, multi-national study. Pediatr Infect Dis J 2014;33:1294–6.
[32] Verma A, Auzinger G, Kantecki M, *et al.* Safety and Efficacy of Anidulafungin for Fungal Infection in Patients with Liver Dysfunction or Multiorgan Failure. Clin Infect Dis 2016; OFID :1-5
[33] Bove KE, Kosmetatos N, Wedig KE et al. Vasculopathic hepatotoxicity associated with E-Ferol syndrome in low-birth-weight infants. JAMA 1985; 254(17): 2422-30.

amiodarone and suspected polysorbate toxicity and a case report of an anaphylactoid reaction in a patient with a history of anaphylactic shock due to intravenous administration of a multivitamin product. [34,35] No case reports of polysorbate toxicity associated with anidulafungin have been reported. A waiver to study neonates was granted to the Applicant because of this potential safety concern. A description of the risk of polysorbate toxicity in neonates is recommended in the Warnings and Precautions section in the ERAXIS USPI, emphasizing that ERAXIS is not approved for use in pediatric patients younger than 1 month of age.

The available pediatric safety data for patients one month of age and older, although limited, is considered adequate based on the safety profile of anidulafungin in study A8851008 and two small PK/safety studies, the clinical experience with anidulafungin use in adults since its approval in 2006, and the known favorable safety profile of the echinocandin class of antifungal drugs.[36,37] The types of adverse reactions observed in pediatric patients was consistent with those previously reported for anidulafungin during its development program and from postmarket safety reports in the applicant's global safety database, and published literature.

In conclusion, anidulafungin exhibits an acceptable safety profile for treatment of candidemia and other forms of invasive candidiasis in pediatric patients, 1 month of age or older, with its risks outweighed by the benefit of anidulafungin in the treatment of a disease with a high mortality risk.

10.12. Conclusions and Recommendations

Efficacy and safety data from Study A8851008 support the use of anidulafungin as a treatment option for invasive candidiasis and candidemia in pediatric patients older than one month of age. The pharmacokinetic data for anidulafungin and polysorbate 80, along with safety and efficacy data, support a dose of 3 mg/kg loading dose followed by 1.5 mg/kg/day for pediatric patients aged 1 month to < 18 years of age. Anidulafungin IV is not recommended for treatment of pediatric younger than 1 month of age (neonates).

No new safety concerns were identified for anidulafungin in the pediatric studies. The TEAEs reported in pediatric patients were consistent with the known safety profile of anidulafungin in adults and the pattern of reported AEs were expected for a seriously ill patient population.

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[34] Masi S, et al. Acute amiodarone toxicity due to an administration error: could excipient be responsible? Br J Clin Pharmacol 2009;67(6):691-3.
[35] Coors EA, et al. Polysorbate 80 in medical products and nonimmunologic anaphylactoid reactions. Ann Allergy Asthma Immunol 2005 Dec;95(6):593-9.
[36] Chen SC-A, Slavin MA, Sorrell TC. Echinocandin antifungal drugs in fungal infections: a comparison. Drugs. 2011;71:11–41.
[37] Kyriakidis I, Tragianidis A, Munchen S, Groll A. Clinical hepatotoxicity associated with antifungal agents. Expert opinion on drug safety 2017;16 (2):149-165.

The safety data including the hepatic safety data for pediatric patients does not change the overall risk/benefit assessment of anidulafungin. Similar to adults, pediatric patients who develop abnormal hepatic laboratory tests on anidulafungin treatment should be monitored for evidence of worsening hepatic tests and evaluated for risk/benefit of continuing therapy.

Efficacy of anidulafungin in the treatment of candidemia / invasive candidiasis in pediatric patients, 1 month of age and older is supported by an adequate and well controlled trial in adults and additional PK, safety and outcome data in pediatric patients.
The safety data from study A8810118, two pediatric PK/safety studies, and the Applicant's global safety database support use of anidulafungin IV, ERAXIS®, for the treatment of candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in pediatric patients, 1 month of age and older.

The results of Study A8851008 are adequate to fulfill Postmarket Requirement 311-1, i.e., Deferred pediatric study under PREA for the treatment of candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in pediatric patients ages, zero months to 16 years of age.

11 Advisory Committee Meeting and Other External Consultations

An FDA Advisory Committee Meeting was not held for this sNDA as input from external experts was not considered necessary.

12 Pediatrics

The pediatric development plan included a determination of the anidulafungin dosage that achieved exposures in pediatric patients similar to that of adults, i.e., efficacy extrapolation based on matching drug exposures and an assessment of the safety of anidulafungin. This sNDA provides PK and safety data to support the treatment indication, i.e. candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in pediatric patients 1 month of age and older.

13 Labeling Recommendations

13.1. Prescription Drug Labeling

13.1.1. Prescribing information

High level changes to the proposed labeling (submitted on 11/22/2020 (S027) and 3/25/20 (S029) are summarized in the Table 13-1 below.

Table 13-1 Summary of Significant Labeling Changes

Section	Applicant's Proposal	Revisions
1. Indications and Usage	• Added an indication of candidemia and ICC to pediatric patients 1 month of age and older • Added a limitation of use to state (b) (4)	• Expanded indication of candidemia and other *Candida* infections (ICC) from adults to pediatric patients, 1 month of age and older. • Added "in adults" qualifier to the indication of treatment of esophageal candidiasis (EC). • Added a limitation of use for the indication of treatment of EC related to high rate of post treatment relapse • Removed limitation of use (b) (4)
2. Dosage and Administration	• Dosage and dosage preparation for pediatric patients	• Provided detailed information regarding dose calculation and preparation of the pediatric infusion to prevent medication errors • Removed (b) (4) and replaced with "Do not Freeze."
4. Contraindications	None	• Added a contraindication for use in patients with known or suspected HFI
5. Warning and Precautions	• Warning regarding ERAXIS	• Added revised warning of

Section	Applicant's Proposal	Revisions
	use in neonates • Warning regarding ERAXIS use in patients with HFI	polysorbate toxicity in neonates • Added revised warning regarding toxicity in patient with HFI (see section 13.1.2)
6. Adverse Reactions	• Added clinical experience with ERAXIS in pediatric patients	• Removed (b) (4) [redacted] • Provided rates for discontinuation in the adult ICC and EC trials
8. Use in Specific Populations		• Expanded pediatric use subsection to include evidence for the efficacy and safety of ERAXIS use for the treatment of candidemia and ICC in pediatric patients 1 month of age and older • Specified that efficacy and safety of ERAXIS for EC treatment in all pediatric patients and ICC treatment in neonates has not been established. • Added a description of ERAXIS-associated risks for polysorbate toxicity and toxicity in patients with HFI
10. Overdosage	• Added a statement (b) (4) [redacted]	• Removed the proposed statement
12. Clinical Pharmacology	• Added PK data in pediatric patients with candidemia/ICC	• Added Cmax to the table • Updated % CV calculations
13. Nonclinical Toxicology	• Added (b) (4) [redacted]	• Removed (b) (4) [redacted]

Section	Applicant's Proposal	Revisions
14. Clinical Studies	• Added data from pediatric candidemia/ICC trial under separate subheading	• Moved data from pediatric candidemia/ICC trial under the candidemia/ICC subheading
16 How Supplied/Storage and Handling		• Moved reconstituted solution stability information to the Dosage and Administration section 2.3
17 Patient Counseling Information	• Added HFI Counseling information	• Added revised HFI counseling information

13.1.2. ADDENDUM: Review of Labeling Supplement (S-029)

Hereditary Fructose Intolerance

On March 25, 2020, the Applicant submitted a prior approval labeling supplement (S-029) to add Hereditary Fructose Intolerance (HFI) in the Warnings and Precautions section of the ERAXIS USPI.

HFI is inherited in an autosomal recessive pattern and is a rare disease caused by catalytic deficiency of aldolase B (fructose-1,6-bisphosphate aldolase).[38,39] HFI is usually identified after dietary exposure to fructose, sucrose, or sorbitol, and typically first manifests at weaning when fructose- and/or sucrose- containing foods are first introduced to children.
Because it is generally identified at weaning, patients below the age of 2 years may be undiagnosed, as they may have heterozygous parents who are unaffected.

Metabolic disturbances (life-threatening hypoglycemia, lactic acidemia, hypophosphatemia, hyperuricemia, hypermagnesemia, and hyperalaninemia) and clinical findings (nausea, vomiting, abdominal distress) can occur when fructose, sucrose or sorbitol are taken orally, either in food or in medicinal preparations. Dietary restriction of fructose, sucrose, and sorbitol is the cornerstone of HFI treatment. Parenteral administration of fructose or sorbitol can be fatal in HFI patients.[38]

[38] Baker P, Ayres L, Gaughan S, et al. Hereditary Fructose Intolerance. 2015 Dec 17. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019.
[39] Ali M, Rellos P, Cox TM. Hereditary Fructose Intolerance. J Med Genet 1998 May;35(5):353-65. doi: 10.1136/jmg.35.5.353

ERAXIS contains fructose (50mg or 100mg per vial) as an inactive ingredient. A contraindication for ERAXIS in patients with HFI or suspected HFI is warranted because infusion of ERAXIS could lead to a metabolic crisis in HFI patients manifested by life-threatening adverse reactions such as (but not limited to) hypoglycemia, hypophosphatemia, seizures, lactic acidosis, renal/hepatic failure. Precipitation of a metabolic crisis in a patient critically ill with invasive candidiasis would likely increase morbidity and mortality. A history of HFI symptoms (nausea, vomiting, abdominal pain) with fructose/sucrose exposure should be obtained prior to administration of anidulafungin. No reports of anidulafungin use in patients with HFI have been reported, however, this is difficult to assess because of the rarity of the disease and anidulafungin is not approved in pediatric patients in the US.

Micafungin does not contain fructose or sucrose could be used as alternative echinocandin for HFI patients with invasive candidiasis. Caspofungin contains sucrose and could cause adverse reactions in patients with HFI. Other treatment options for patients with HFI and candidemia/invasive candidiasis include triazoles and amphotericin B. There is another rare inborn of fructose metabolism, i.e. fructose -1,6 -bisphosphatase/ fructose- 1,6- disphosphatase deficiency[40]; however, a high load of fructose (at least 1g/kg is necessary to cause a metabolic crisis) is not achievable with the currently approved dose of ERAXIS (a maximum of 3 mg/kg/day) to merit inclusion as a contraindication or a warning.

Clinical reviewer's comment: *The proposed labeling for HFI was discussed with P. Smpokou M.D., Acting Deputy Director in the Division of Rare Diseases & Medical Genetics (DRDMG). Labeling discussions were ongoing with the Applicant at the time this review was completed.*

The following labeling changes are recommended in HIGHLIGHTS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS:

HIGHLIGHTS
CONTRAINDICATIONS
- Patients with Hereditary Fructose Intolerance (HFI) (4, 5.4)

WARNINGS AND PRECAUTIONS

- Hereditary Fructose Intolerance (HFI): ERAXIS contains fructose. Risk of metabolic crisis with life-threatening hypoglycemia, hypophosphatemia, lactic acidosis, and hepatic failure. Obtain history of HFI symptoms in pediatric patients before ERAXIS administration. (5.4)

[40] Sunita Bijarnia-Mahay, Sameer Bhatia, and Veronica Arora, editors. Fructose-1,6-Bisphosphatase Deficiency. GeneReviews® [Internet].

FULL PRESCRIBING INFORMATION

CONTRAINDICATIONS

ERAXIS is contraindicated in:

- Patients with Hereditary Fructose Intolerance (HFI) [*see Warnings and Precautions* (5.4)]

WARNINGS AND PRECAUTIONS

5.4 ERAXIS contains fructose, an inactive ingredient, and may precipitate a metabolic crisis that may include, but is not limited to life-threatening hypoglycemia, hypophosphatemia, lactic acidosis, and hepatic failure in patients with HFI. Obtain careful history of HFI symptoms (nausea, vomiting, abdominal pain) with fructose/sucrose exposure prior to ERAXIS administration because a diagnosis of HFI may not yet be established in pediatric patients [see Contraindications (4) and Use in Specific Populations (8.4)].

14 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

15 Postmarketing Requirements and Commitment

- There are no requirements for an additional postmarket study(ies).
- The results from Study A8851008 fulfill the Postmarket Requirement 311-1 from 2006: Deferred pediatric study under PREA for the treatment of candidemia and other forms of *Candida* infections (intra-abdominal abscess and peritonitis) in pediatric patients ages, zero months to 16 years of age. A waiver to study pediatric patients from birth to 1 month was previously granted.

16 Division Director (Clinical) Comments

I agree with the review team's assessment and conclusions.

17 Appendices

17.1. References

See references in footnotes.

17.2. Financial Disclosure

The applicant provided a list of the trial investigators and any investigators with disclosable financial interests. Nine of the 156 investigators had a stated financial interest or arrangement. The Applicant certified that they had acted with due diligence to obtain the information required from the listed 156 investigators.

Covered Clinical Study (Name and/or Number): A8851008

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 156		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 9		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 9 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 147		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

17.3. OCP Appendices (Technical documents supporting OCP recommendations)

Pharmacometrics Review

Applicant's population PK analysis

With the current submission, the Applicant submitted one clinical study (Study A8851008) to support the extension of ICC indication to pediatric patients age down to 1 month of age. To describe the anidulafungin PK in the target patient populations, the applicant performed population PK analysis (popPK) analysis based on the data from a total of 4 studies including the pediatric study (A8851008) and two adult studies conducted in patients with invasive candidiasis, including candidemia (ICC). Also, the PK data (intensive PK) in infants and neonates with suspected serious infections from a Duke IIR study were included in the PK analysis as the anidulafungin data in pediatric subjects under 2 years of age were limited in Study A8851008. Studies included in popPK analysis are listed in the table below.

Study	Design	Dose (LD/MD)	Treatment Duration*
A8851008	Phase 3b, prospective, open-label, non-comparative study in pediatric patients aged 1 month to <18 years with ICC	IV anidulafungin: 3.0 mg/kg LD/1.5 mg/kg MD (not to exceed 200 mg LD/100 mg MD) QD, a minimum of 10 days before switching to oral fluconazole, with the exception of subjects who were enrolled under Amendment 9, without microbiologically-confirmed *Candida* infection, who were to receive a minimum of 5 days of anidulafungin treatment	14-49 days
A8851011	Phase 4, prospective, open-label, non-comparative study for the treatment of ICC in neutropenic and non-neutropenic adult patients (≥ 18 years) with *Candida* infections	IV anidulafungin: 200 LD/100 mg MD QD, a minimum of 5 days before switching to oral azole therapy	14-42 days
A8851019	Phase 3b, prospective, open-label, non-comparative study for the treatment of documented ICC in intensive care unit adult patients (≥ 18 years)	IV anidulafungin: 200 mg LD/100 mg MD QD, a minimum of 10 days before switching to oral fluconazole therapy	14-56 days
Duke IIR **	Phase 1, prospective, open-label, non-comparative, single-center, PK study in infants and neonates (<24 months) with suspected serious infections	IV anidulafungin: 3.0 mg/kg LD/1.5 mg/kg MD QD	3 to 5 days

ICC: invasive candidiasis including candidemia; PK: pharmacokinetic.
LD: loading dose; MD: maintenance dose; QD: once daily; IV: intravenous
IIR: Investigator-Initiated Research;
* treatment duration includes fluconazole therapy after switch from anidulafungin;
** Only included in population PK analysis with permission. Since it was primarily designed as a PK study, it was excluded for exposure-efficacy and exposure-safety analyses.
Source: Applicant's popPK report, Table 1, page 26.

Baseline patient characteristics of the PPK dataset are summarized for the 4 studies in Table 17-1. Six subjects in the 1 month to < 2 years age group in Study A8851008 and 22 adult subjects in Study A8851019 had intensive PK samples.

Table 17-1. Summary of Number of Subjects and PK samples and Demographics of popPK population

	Duke IIR	A8851008	A8851011	A8851019[a]	Total
Number of Subjects	14	66	33	50	163
Number of PK Samples	110	281	123	283	797
Sex					
Number (%) of Males	9 (64.29)	36 (54.55)	20 (60.61)	30 (60)	95 (58.28)
Number (%) of Females	5 (35.71)	30 (45.45)	13 (39.39)	20 (40)	68 (41.72)
Race					
Number (%) of White	10 (71.43)	52 (78.79)	26 (78.79)	48 (96)	136 (83.44)
Number (%) of Black	4 (28.57)	1 (1.52)	4 (12.12)	1 (2)	10 (6.13)
Number (%) of Asian	0 (0)	6 (9.09)	2 (6.06)	0 (0)	8 (4.91)
Number (%) of Other	0 (0)	7 (10.61)	1 (3.03)	0 (0)	8 (4.91)
Age (years)					
Mean (SD)	0.225 (0.34)	5.861 (5.14)	53.182 (18.83)	58.18 (13.74)	31.006 (28.38)
Median (Range)	0.072 (0.005-1.236)	4 (0.099-17)	59 (20-81)	58.5 (25-80)	21 (0.005-81)
Body Weight (kg)					
Mean (SD)	3.23 (2.61)	22.99 (19.09)	77.78 (19.37)	73.83 (27.31)	47.98 (35.51)
Median (Range)	2.8 (0.75-9.47)	16.6 (2.31-85.7)	77.2 (37.8-122.1)	70 (48-240)	54 (0.75-240)

Source: Applicant's popPK report. Table 6, page 37.

The popPK analysis was conducted using the nonlinear mixed-effects modeling approach. The software packages NONMEM, version 7.3 (b) (4) and PsN version 4.2.0 were used as supporting software for the execution of NONMEM. R version 3.4.1 was used for data manipulation, exploratory data analysis and creation of graphs.

The final popPK model (run15) was a two-compartment disposition model with first order elimination and parameter estimates are presented in Table 17-2 For a typical subject with body weight of 70 kg, CL, Vc, Vp, and Q were estimated to be 1.16 L/h, 26.7 L, 22.4 L, and 2.37 L/h, respectively. The IIVs for CL, Vc, Vp and Q were 37.9%, 46.5%, 53.8% and 52.2% respectively. The shrinkage for IIV on CL and Vc was relatively small (< 11%). The Applicant noted that the large shrinkage for Vp and Q could be due to lack of data in the middle of the dose interval. Body weight was a structural covariate on PK parameters indicating that CL, Vc and Vp increased with increases in body weight. From covariate analyses, neither age nor sex had a statistically significant effect on CL and Vc. Race was not investigated because more than 80% of the population was white.

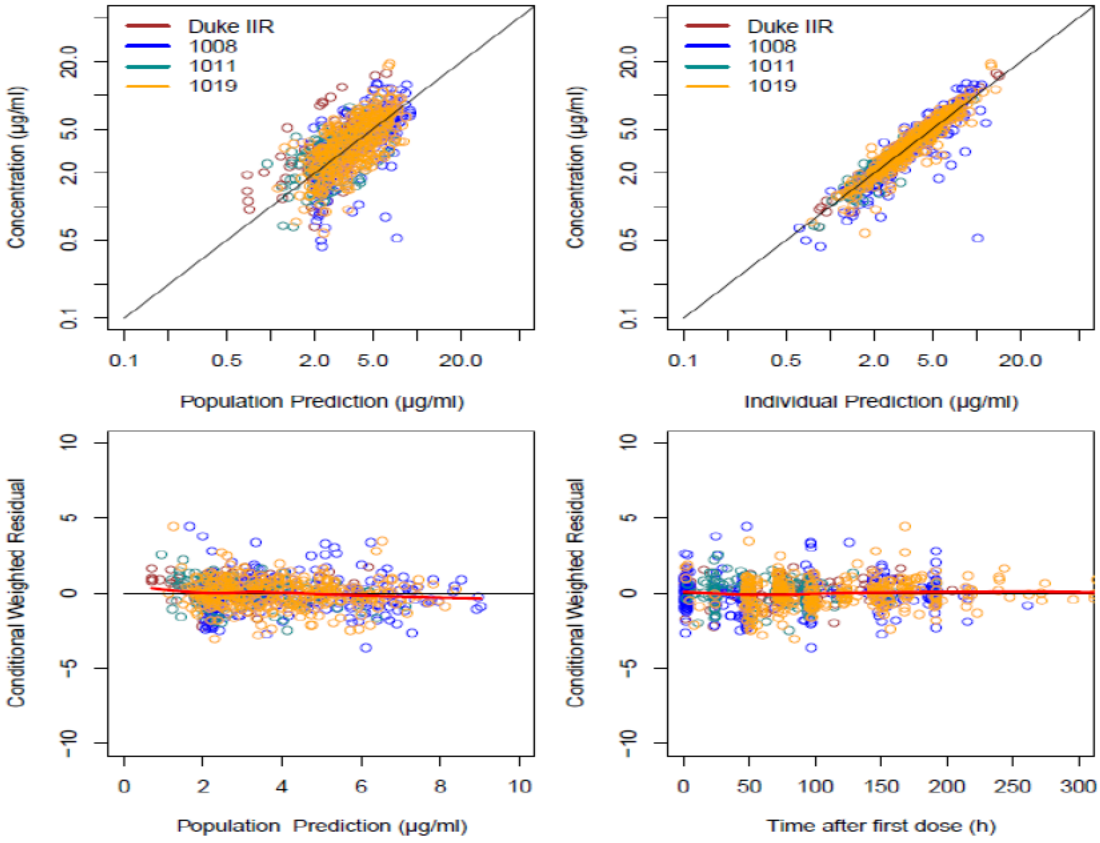
Table 17-2. Parameter Estimates of Final popPK model

Parameter		Estimate (%RSE)	Shrinkage (%)
CL [a]	L/h	1.16 (3.92)	
Vc [a]	L	26.7 (6.5)	
Q [a]	L/h	2.37 (15.2)	
Vp [a]	L	22.4 (12.9)	
WT on CL		0.915 (2.98)	
WT on Vc		1.2 (4.95)	
WT on Vp		0.769 (6.04)	
IIV on CL	%	37.9 (7.31)	5.37
IIV on Vc	%	46.5 (19.9)	10.3
corr CL-Vc [b]		0.16 (0.0947)	
IIV on Q	%	52.2 (18.6)	54.6
IIV on Vp	%	53.8 (14.5)	44.7
Residual Error	%	21.2 (6.77)	15.9

Source: Applicant's popPK report. Table 8, page 40.

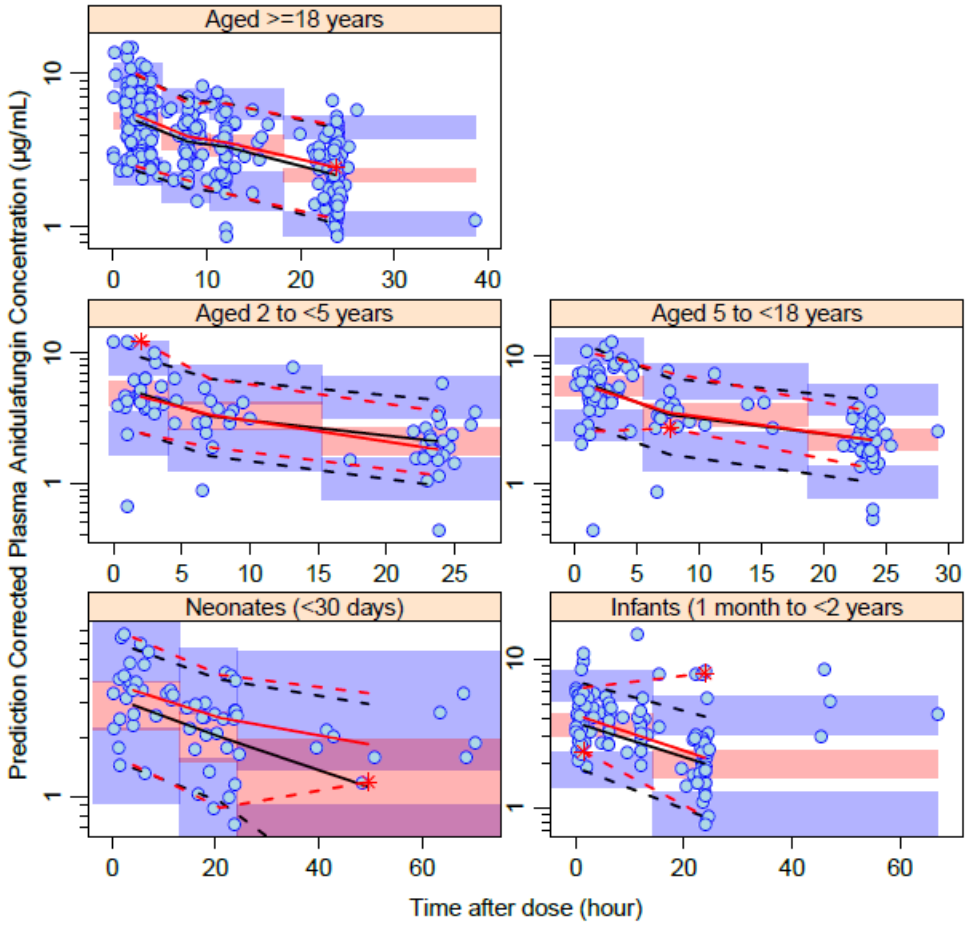
Standard goodness of fit plots stratified by study (color) are presented in **Figure 17-1**. The prediction corrected visual predictive check (pcVPC) plot stratified by the age group is presented in **Figure 17-2**.

Figure 17-1. Goodness of Fit for the Final model by Studies



Source: Applicant's popPK report. Figure 3, page 41.

Figure 17-2. Prediction Corrected Visual Predictive Check Stratified by Age Group



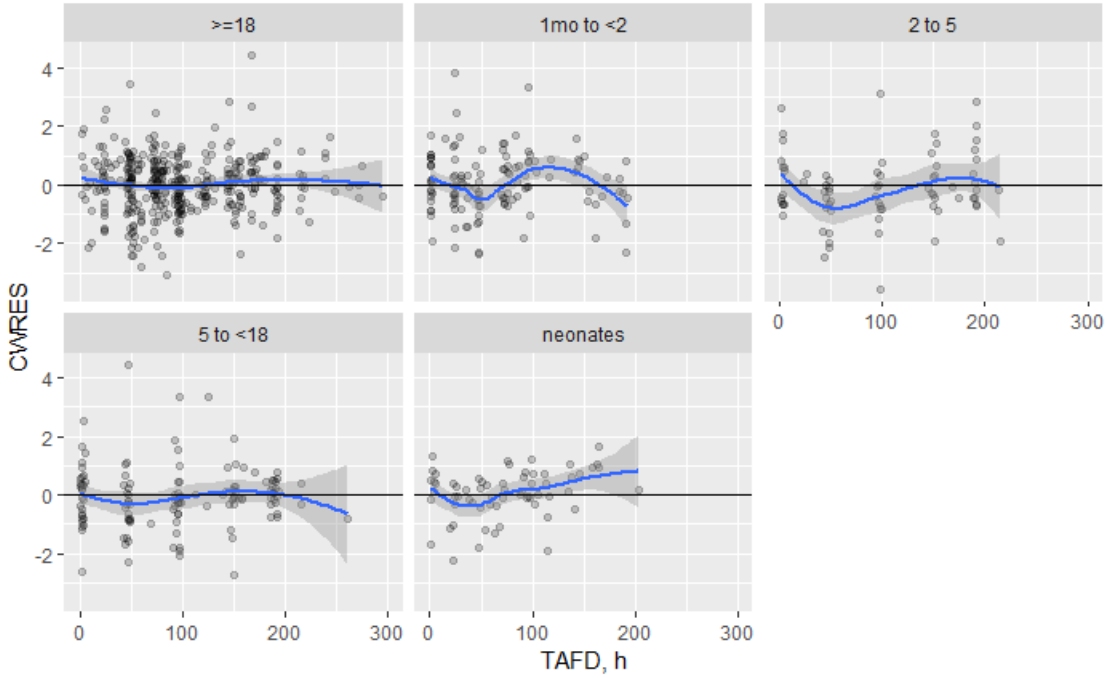
Red and black dashed lines present 90% CI (95% upper limits and 5% lower limits) of observed and simulated data, respectively. Red and black solid lines are median (50%) of observed and simulated data, respectively. Blue dots are observed data. Shadow areas are 95% CI.
Source: Applicant's popPK report. Figure 6. Page 45.

Reviewer's Assessment on popPK analysis

The Applicant's popPK model adequately describes the observed concentrations in pediatric population across age groups and adult population.

- Parameter estimates for the final model were estimated with acceptable precision with relative standard error (RSE) (all <20%) and the shrinkage for IIV on CL and Vc were <20%.
- In the reviewer's examination of GOF plots stratified by study and age groups, no obvious bias was not noted in general. The reviewer noted a slight overprediction in Day 3 pre-dose samples in younger age group (<5 years old) (Figure 17-3), which indicates the actual drug CL may be higher at earlier doses (i.e., 2nd dose) than the estimated CL. This trend is not notable in the later doses; hence, the steady-state exposure estimation is not likely affected by this overprediction.

Figure 17-3. CWRES vs. Time after First Dose by Age Groups



- ETAs for CL, Vc, Q and Vp were centered around zero without obvious bias (Applicant's report. Figure 4).
- The applicant's pcVPC plots (**Figure 17-2**) shows a good agreement between the central tendency (median), and the 90% prediction band for the observed and simulated data across the age group.

Applicant's Assessment of Anidulafungin Exposure in Pediatric Patients vs. Adult ICC patients
The Applicant calculated exposure parameters at steady state $AUC_{0\text{-}24,ss}$ and $C_{min,ss}$ using the individual parameter estimates obtained from the final PK model using the equations presented in Applicant's popPK report page 35-36. The exposures ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$ and $C_{min,ss}$) summarized by age groups across all 4 studies are presented in Section 6. The geometric mean ratios (GMR) for $AUC_{0\text{-}24,ss}$ in the various pediatric age groups range from 0.90 to 0.98 that of adults. Cmax,ss is generally higher in infants and older children (1.12 to 1.20). PK summary of ICC pediatric patients from Study A8851008 (the pivotal pediatric study) are presented in Section 6. The geometric mean ratio for the infants (1 month to < 2 years) compared to adult PK was 0.83.

Reviewer's Assessment on Anidulafungin Exposure in Pediatric Patients
The steady-state exposures across the age groups are largely within the range of those in adults. The review team concluded that the proposed dosing regimen provides comparable exposures for pediatric patients ages 1 month to <18 years old compared to those in adults. The following are key elements of the pharmacometrics reviewer's approach to evaluate the adequacy of the proposed dosing regimen in pediatric patients:

- A slightly lower exposure in the infant group (1 month to < 2 years) compared to adults was noted: the geometric mean ratios (GMRs) were 0.91 for $AUC_{0\text{-}24,ss}$, and 0.9 for Cmin,ss based on the combined data from DUKE IIR study and Study A8851008 and the GMRs were 0.81 for $AUC_{0\text{-}24,ss}$, and 0.78 for $C_{min,ss}$ based on the Study A8851008. As there is no clear E-R relationship at the proposed dosing regimen for pediatric patients (See the next section for E-R analyses), this difference is not clinically relevant in terms of efficacy.
- Sensitivity analyses (Table 17-3) were performed by 1) excluding the one subject who had an extremely high exposure value (AUC of 260.64 ug*h/mL), and 2) excluding the two subjects data who received only one loading dose (3 mg/kg) prior to discontinuation and the exposure metrics were calculated based on the first dose. In these sensitivity analyses, there is no obvious change in exposure in each age group.

Table 17-3. Geometric Means (%CV) of Anidulafungin Exposure by Age Groups (Sensitivity Analysis)

	Excluding data from 1 subject with outlier exposure[A]			**Excluding data from 2 subjects who received only one dose[B]**		
	AUC (%CV)	Cmin (%CV)	Cmax (%CV)	AUC (%CV)	Cmin (%CV)	Cmax (%CV)
neonates	75.3 (46)	2.4 (53)	4.7 (35)	75.3 (46)	2.4 (53)	4.7 (35)
1mon to <2yr	72.2 (28)[A]	2.1 (35)[A]	6.4 (27)[A]	76.3 (39)	2.2 (46)	6.7 (34)
2 to <5yr	77.3 (40)	2.3 (46)	6.6 (43)	74.9 (38)[B]	2.2 (45)[B]	6.4 (42)[B]
5 to <18yr	81.9 (36)	2.4 (41)	6.2 (30)	79.5 (32)[B]	2.3 (37)[B]	6.1 (28)[B]
Adult PK	84.1 (42)	2.5 (45)	5.6 (45)	84.1 (42)	2.5 (45)	5.6 (45)

A: one subject (b) (6) from DUKE IIR study
B: one subject (b) (6) and other subject (b) (6) in Study A8851008
Source: Reviewer's table based on the Applicant's dataset expo.xpt

- There is a notable discrepancy in infant (1 month to < 2 years) exposure between DUKE IIR study and Study A8851008. It was not feasible to evaluate the effect of each baseline characteristics (age, weight, and disease status) on PK due to the small dataset (6 infants from DUKE IIR study). One contributing factor is the highest exposures (AUC = 261 µg*h/mL and Cmin =8.2 µg/mL) from one infant subject from DUKE study, which results in the higher exposure for DUKE study compared to Study A8851008.

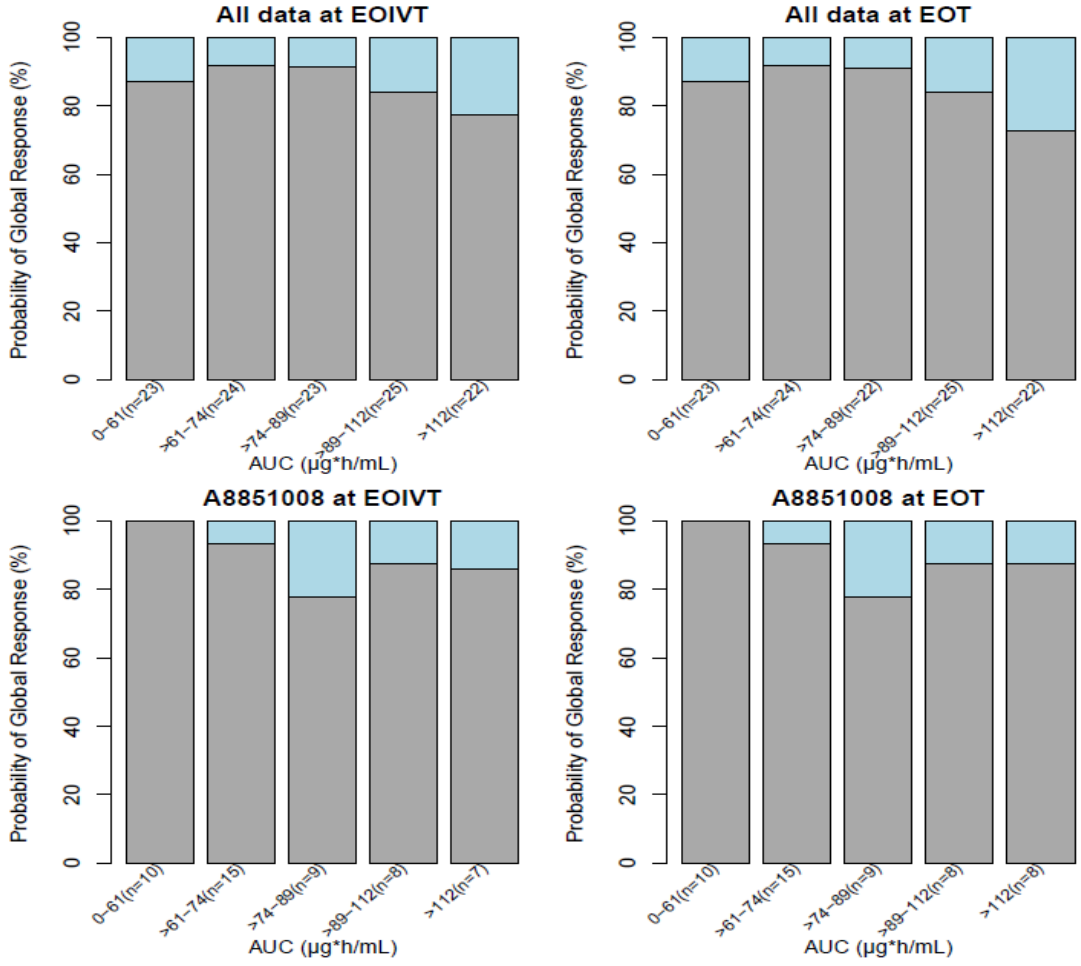
Applicant's E-R analysis for Efficacy

E-R analysis was conducted using data from the efficacy population which consisted of the mITT population (a total of 484 subjects [64 pediatrics and 420 adults] with confirmed *Candida* infection who received at least one dose of study drug in the two adult studies (A8851011, A8851019) and the pivotal pediatric study (A8851008). A total of 134 subjects within this population had matched estimated exposure parameters and efficacy data and were included for E-R analysis. There were 121 subjects with MIC data available for the baseline pathogen.

The evaluated efficacy endpoints included global response (success vs. failure) at EOIVT and EOT, and all-cause mortality (alive vs. died) during study therapy period EOT (including IV and oral) and EOS including follow up period. The exposure metrics evaluated included $AUC_{0\text{-}24,ss}$, $C_{min,ss}$ and $AUC_{0\text{-}24,ss}$ /MIC.

The applicant's E-R analysis shows that there are no clear relationships between anidulafungin exposure parameters and efficacy in pediatric and adult subjects with ICC. The global response of failure does not appear to be related to lower anidulafungin exposure in both overall population and Study A8851008 (**Figure 17-4**). Probability of death does not appear to be related to low exposure in both overall population and Study A8851008. In the graphical examinations, there was a substantial overlap in anidulafungin exposures ($AUC_{0\text{-}24,ss}$, $C_{min,ss}$ and $AUC_{0\text{-}24,ss}$ /MIC) among the global responses of success, failure, and indeterminate (Applicant's popPK report page 54-56, Figure 10-12). The anidulafungin exposures in subjects who had died overlapped with those in subjects who were alive at EOT and EOS. (Applicant's popPK report page 60-62, Figure 14-16).

Figure 17-4. Probability of Global Response vs. AUC0-24,ss at EOIVT and EOT for All Data (Upper Panel) and Study A8851008 (Lower Panel)



Source: Applicant's popPK report. Figure S1, page 9. Grey areas are the probability of success and the blue areas are the probability of failure. Indeterminate data were excluded.

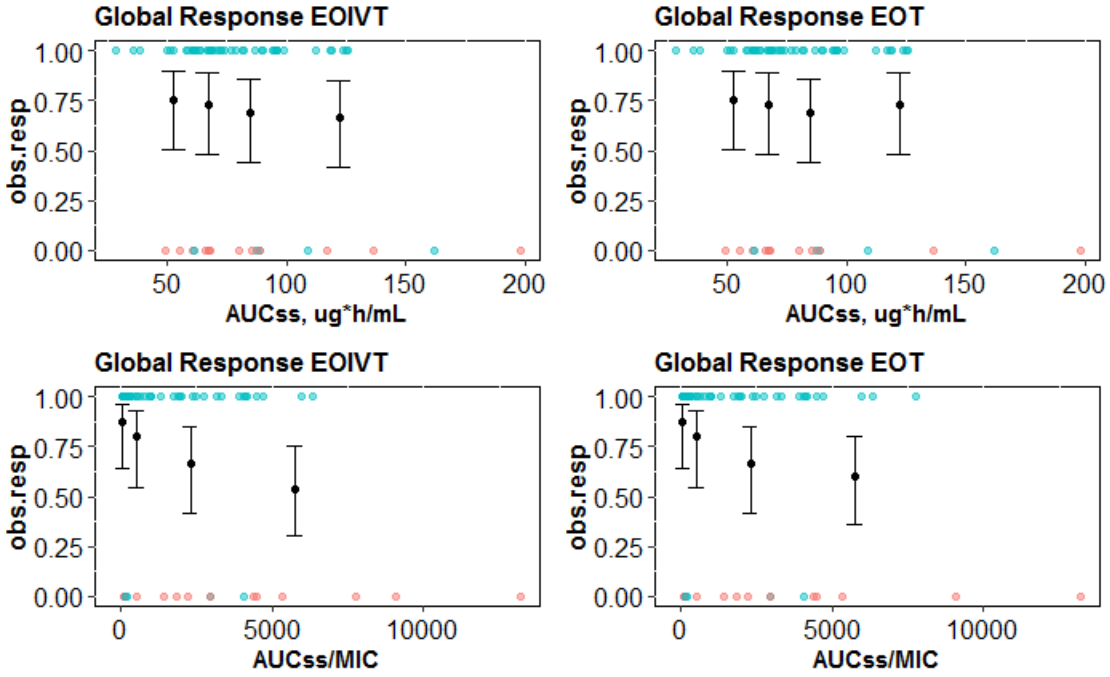
Reviewer's Assessment of E-R for Efficacy

The reviewer agrees with the Applicant's conclusion that there is no clear E-R relationship in the observed exposure range. It is important to note that there has not been an E-R relationship established for ICC indication in adult patients to date. To support the extension of ICC indication to the pediatric patients for this pediatric efficacy supplement submission, the Applicant performed the E-R analyses based on the two adult studies (A8851011 and A8851019) combined with the pediatric study (A8851008). The reviewer noted that these two adult studies are open-label, and uncontrolled studies and have not been previously reviewed by FDA, hence the appropriateness of efficacy assessment is unknown. Therefore, the E-R relationship observed in these studies is considered as exploratory.

The reviewer performed an exploratory E-R analysis only based on the data from 64 pediatric patients from Study A8851008. Logistic regressions were fitted between the exposure metrics ($AUC_{0\text{-}24,ss}$, and $AUC_{0\text{-}24,ss}$ /MIC) with the success rate at EOVIT or EOT (**Figure 17-5**). In this analysis, "Indeterminate" outcomes were treated as "failure" (note that on the Applicant's analysis, data for indeterminate outcomes were excluded). Similar to the Applicant's descriptive analysis, no attenuation in efficacy was evident at the lower exposures observed in the infant age group (1 month to < 2 years) in Study A8851008.

However, E-R analysis for pediatric patients shows that a lower efficacy rate (in global response at EOVIT or EOT) appears to be associated with a higher exposure. Note that "indeterminate" outcomes which comprised ~20% of the E-R dataset were treated as non-responders and the impact of these data was not accounted in this analysis. Also, the causal relationship of this trend cannot be explained by the present analysis. Any potential confounding covariates (i.e., disease severity and underlying comorbidities) leading to this trend could not be evaluated due to the small number of subjects for each potential covariate.

Figure 17-5. E-R relationships observed in Pediatric Patients in Study A8851008



Applicant's E-R analysis for Safety

The Applicant conducted E-R analysis for safety to evaluate the relationships between anidulafungin exposures and the incidence of anidulafungin treatment emergent all-causality hepatic or GI AEs. The E-R analysis was performed based on safety data from 149 subjects who had analyzable PK samples from the two adult studies (A8851011, A8851019) and the pivotal pediatric study (A8851008). Hepatic AEs included hepatobiliary disorders (cholestasis, hepatitis acute, hepatomegaly, hyperbilirubinemia, and ocular icterus) and investigations (ALT/AST increased, gamma-glutamyltransferase increased, liver function test abnormal/increased, prothrombin time prolonged, and transaminases increased). GI AEs included nausea, vomiting, diarrhea, abdominal pain and abdominal distension. Hepatic/GI AEs were counted only if emergent during the anidulafungin treatment period in this exposure-response analysis.

In the pooled analysis using pediatric and adult data, there does not appear to be any exposure relationship for all-causality GI AEs. No statistically significant associations between anidulafungin exposures and hepatic or GI AEs were identified using either linear or E_{max} relationship. There appears to be a slight trend towards an increased incidence of all-causality hepatic AEs with higher exposure in the overall population.

In the analysis based on pediatric patients only (Study A8851008), a total of 66 subjects had PK samples and were included in exposure-safety analyses. Twelve (18.18%) subjects and 27 subjects (40.91%) reported hepatic and/or GI AEs emergent during anidulafungin treatment,

respectively. Descriptive analyses did not show any trend between anidulafungin exposures and hepatic or GI AEs.

Reviewer's Comment:
The Applicant's pooled E-R analysis for safety is considered exploratory. This analysis was performed based on the safety data from the two adult studies in addition to the data from the pivotal pediatric study (A8851008). It should be noted that the adult studies (A8851011, A8851019) have not been previously reviewed by FDA and the appropriateness of the safety assessments is unknown. Also, small portions (12% and 23%) of subjects who had paired PK samples from the studies A8851011, and A8851019, respectively, were included in the analysis.

17.4. Additional Clinical Outcome Assessment Analyses

A summary SAEs by subject is presented in **Table 17-4**. Three SAEs were assessed as related to treatment with anidulafungin as discussed in section 10.4.2. No other SAEs were assessed as related to anidulafungin or fluconazole. The majority of SAEs reported in pediatric patients had an outcome of recovered/resolved.

Table 17-4 Study A8851008: Serious Adverse Events by Subject ID – Safety Population

Unique Subject Identifier	Age / Age Units / Sex	Dictionary-Derived Term	Study Day of Start of Adverse Event / Study Day of End of Adverse Event
(b) (6)	10 / YEARS / F	Mental status changes	18 / 22
		Febrile neutropenia	46 / 63
		Pharyngitis streptococcal	46 / 57
		Staphylococcal bacteremia	46 / 57
		Brachiocephalic vein thrombosis	46 / 117
	10 / YEARS / F	Urinary tract infection	33 / 43
	9 / MONTHS / M	Abdominal sepsis	3 / 31
	4 / YEARS / F	Unintentional medical device removal	7 / 8
		Hypoglycemia	31 / 31

Unique Subject Identifier	Age / Age Units / Sex	Dictionary-Derived Term	Study Day of Start of Adverse Event / Study Day of End of Adverse Event
(b) (6)	10 / YEARS / F	Urinary tract infection	26 / 49
	10 / YEARS / M	Oral herpes	43 / 46
	7 / MONTHS / F	Pancytopenia	10 / 14
	4 / YEARS / F	Staphylococcal bacteremia	25 / 28
		Device related infection	36 / 55
	33 / MONTHS / M	Respiratory distress	15 / 42
	16 / YEARS / M	Seizure	12 / 14
	16 / YEARS / F	Septic shock	13 / 17
	6 / YEARS / M	Acute respiratory distress syndrome	4 / 4
	30 / MONTHS / M	Catheter site infection	30 / 39
		Staphylococcal bacteremia	42 / 45
	9 / YEARS / M	Pancreatic pseudocyst	1 / 21
		Pancreatic pseudocyst	29 / 34
	11 / YEARS / M	Meningitis	9 / 31
	17 / YEARS / M	Gastrointestinal hemorrhage	15 / 18
		Sepsis	16 / 18
	7 / YEARS / M	Septic shock	11 / 20
	31 / MONTHS / F	Hemorrhage intracranial	36 / 36
	4 / YEARS / F	Respiratory failure	17 / 20
		Aspiration bronchial	17 / 20
	3 / YEARS / M	Septic shock	1 / 1

Unique Subject Identifier	Age / Age Units / Sex	Dictionary-Derived Term	Study Day of Start of Adverse Event / Study Day of End of Adverse Event
(b) (6)	11 / YEARS / F	Herpes zoster	29 / 34
	12 / YEARS / F	Pneumonia	2 / 4
		Acute respiratory failure	2 / 4
		Escherichia infection	3 / 4
		Metabolic acidosis	3 / 4
	27 / MONTHS / M	Herpes zoster	46 / 53
	5 / YEARS / M	Transaminases increased	10 / 12
	4 / YEARS / F	General physical health deterioration	33 / 43
	16 / MONTHS / F	Streptococcal sepsis	35 / 49
	3 / YEARS / F	Diarrhea	1 / 6
	28 / MONTHS / M	Device related infection	30 / 47
	1 / YEARS / M	Coagulopathy	5 / 7
	7 / YEARS / F	Pneumonia	20 / 23
		Febrile neutropenia	34 / 39
		Lower respiratory tract infection	45 / 48
		Sepsis	45 / 48

Source: OCS Analysis Studio, Listing Tool.
Subjects - Dataset: Demographics; Filter: SAFFL = 'Y'.
Events - Dataset: Adverse Events; Filter: AESER = 'Y', TRTEMFL = 'Y'. Age: Age calculated

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/s/

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TERRY J MILLER
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KAREN M HIGGINS
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YULIYA I YASINSKAYA
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DAKSHINA M CHILUKURI
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PHILIP M COLANGELO
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JUSTIN C EARP
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ELIZABETH M OSHAUGHNESSY
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ABIMBOLA O ADEBOWALE
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MAUREEN P DILLON PARKER
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