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Safety, Efficacy and Pharmacokinetics of Anidulafungin in Patients 1 Month to <2 Years of Age With Invasive Candidiasis, Including Candidemia

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Abstract: Nineteen patients 1 month to <2 years of age with (n = 16) or at high risk of (n = 3) invasive candidiasis received anidulafungin for 5–35 days (3 mg/kg day 1, 1.5 mg/kg daily thereafter) followed by optional fluconazole (NCT00761267). Most treatment-emergent adverse events were mild/moderate, and no treatment-related deaths occurred. End of intravenous therapy global response success rate was 68.8%. Pharmacokinetics were similar to adult patients.

Key Words: anidulafungin, invasive candidiasis, candidemia, pediatric, echinocandin

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Availability of Data and Material: Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Candida species are a common cause of invasive fungal infection in hospitalized patients, including children.[1] Invasive candidiasis (IC) has been associated with excessive mortality and long-term sequelae in infants.[2] Anidulafungin is an echinocandin antifungal drug licensed in adults for the treatment of candidemia and other forms of *Candida* infections.[3]

We conducted a prospective, open-label, noncomparative, multicenter, international study (NCT00761267) to evaluate the safety, efficacy and pharmacokinetics (PKs) of anidulafungin for the treatment of IC, including candidemia, in pediatric patients 1 month to <18 years of age. Data in patients 2 to <18 years of age from this study have been published previously.[4] Here, we report data for anidulafungin in patients 1 month to <2 years of age, including the results of PK subanalyses of anidulafungin and polysorbate 80 (PS80)—a solubilizing agent for anidulafungin.

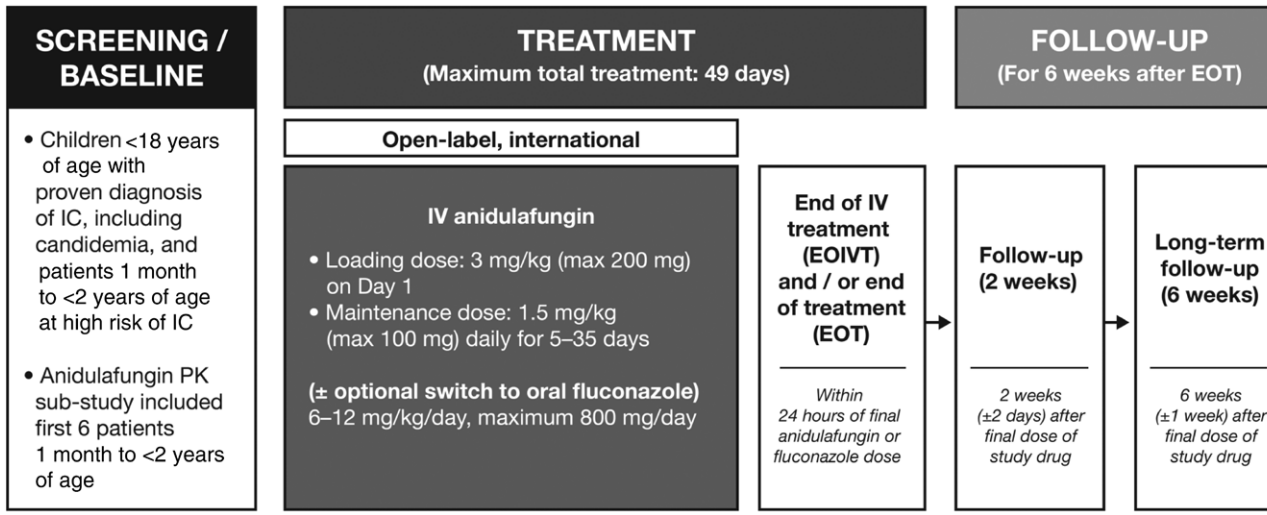
MATERIALS AND METHODS

The study design is presented in Figure 1. Patients with IC, 1 month to <18 years of age, were enrolled from June 2009 to February 2018. Full inclusion and exclusion criteria were published previously.[4] The inclusion criteria were revised to permit the participation of patients at high risk for IC (without microbiologically confirmed IC) to facilitate enrollment of patients in the 1 month to <2 years of age group. Additionally, exclusion criteria were amended to allow the enrollment of patients who received prior systemic antifungal therapy and patients for whom removal of an infected catheter was undesirable.

The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines established by the International Council for Harmonization. Written consent from parents or legal guardians was obtained.

All patients received a 3 mg/kg loading dose of intravenous (IV) anidulafungin on day 1, followed by a maintenance dose of 1.5 mg/kg daily (both infused at ≤1.1 mg/min) administered for ≤35 days. An optional switch to oral fluconazole (6–12 mg/kg/d, maximum 800 mg/d) was allowed up to a maximum total treatment duration (anidulafungin plus oral fluconazole) of 49 days. This switch was permitted after a minimum of 10 days of anidulafungin in patients with microbiologically confirmed IC. Patients at high risk of IC (without microbiologically confirmed IC) could be switched to oral fluconazole after a minimum of 5 days.

The primary objective[4] was to assess the safety and tolerability of anidulafungin in children with IC. Secondary objectives included global response at end of IV therapy (EOIVT), end of treatment, and at the week 2 and week 6 follow-up visits.[4] We also assessed relapse and new infection rates, at the week 2 and week 6 follow-up visits, and all-cause mortality throughout the study. Additionally, we examined the PK of anidulafungin and PS80. The first 6 patients were included in a PK substudy with



IC, invasive candidiasis; IV, intravenous; PK, pharmacokinetic.

FIGURE 1. Study design.

serial PK samples collected on days 1 and 2 and analyzed using noncompartmental methods to confirm the dosage regimen. Serial blood samples were collected at 6 time points on days 1 and 2: 2 minutes before the end of infusion on day 1 (receiving 3 mg/kg); and, on day 2 (receiving 1.5 mg/kg), just before the start of infusion, 2 minutes before the end of infusion, and 6, 12 and 24 hours after the start of infusion.

Plasma samples were stored at −20°C or colder after collection and analyzed periodically at a centralized laboratory (PPD, Richmond, VA) using a validated high-performance liquid chromatography–tandem mass spectrometric method. The bioanalytical assay had a dynamic range of 50–20,000 ng/mL and a lower limit of quantification of 50 ng/mL for anidulafungin. The between-day assay accuracy, expressed as percent relative error for quality control (QC) concentrations, ranged from −10.6% to 4.17%. Assay precision, expressed as the between-day percent coefficients of variation (% CV) of the mean estimated concentrations of QC samples, was ≤8.68%.

Blood samples for PS80 measurements were collected from 8 patients following a request from the European Medicines Agency for exposure data of PS80 in infants. Blood samples were collected at 3–5 of the following time points: day 1 (0–2 hours postdose); day 3 (predose); day 5 (0–3 hours postdose); day 7 (6–12 hours delayed postdose); and day 9 (predose).

Plasma samples were stored at −20°C or colder after collection and analyzed periodically at a centralized laboratory (PPD) using a validated high-performance liquid chromatography–tandem mass spectrometric method. The bioanalytical assay had a dynamic range of 5.00–100 µg/mL and a lower limit of quantification of 5.00 µg/mL for PS80. The between-day assay accuracy, expressed as percent relative error, for QC concentrations, ranged from 2.96% to 6.01%. Assay precision, expressed as the between-day % CV of the mean estimated concentrations of QC samples, was ≤11.2%.

Anidulafungin global response was evaluated in the modified intent-to-treat population only (patients who received at least 1 dose of study drug and had confirmed *Candida* infection). Statistical analyses were mainly descriptive, as detailed previously.[4]

RESULTS

Nineteen patients were enrolled at 13 sites in 7 countries. All were white, 10 (52.6%) were male, and the mean age was 0.9 years (range: 0.1–1.8 years). All received IV anidulafungin and were included in the safety population. Six patients were switched to fluconazole treatment (see Table 1 for treatment durations).

Sixteen of 19 patients (84.2%) had microbiologically confirmed IC and were included in the modified intent-to-treat population. Baseline pathogen data are summarized in Table 2. The most common site of infection was blood (15/16, 93.8%), and the most common risk factor for IC was the use of broad-spectrum antibiotics, which was reported in all patients (Table 1).

Seventeen of 19 patients (89.5%) exhibited treatment-emergent events (TEAEs) of any causality. TEAEs affecting >20% of the overall safety population are detailed in Table 2. Events were all mild-to-moderate in severity except 10 severe TEAEs reported in 7 patients (36.8%). Of these, 5 were considered serious (abdominal sepsis, coagulopathy, diarrhea, pancytopenia and urinary tract infection), and 1 was considered related to anidulafungin treatment (diarrhea); all resolved. A summary of all-causality TEAEs affecting >5% to ≤20% of patients is in Table 3.

Three patients (15.8%) experienced a total of 5 treatment-related TEAEs: diarrhea, pyrexia, increased alanine transaminase, increased aspartate transaminase and erythema. Of these, only diarrhea (serious adverse event in a 3-month-old girl resolved) led to discontinuation of anidulafungin. This event was considered to be anidulafungin related. No patients experienced TEAEs related to fluconazole.

Regarding all-cause mortality, 1 of 19 patients (5.3%) died during the study. The cause of death in this 16-month-old boy was multiple organ dysfunction syndrome on study day 40 which was not considered treatment related.

Eleven of 16 patients (68.8%) achieved a global response of success at EOIVT (Table 2). Responses by the site of infection and by neutrophil count are summarized in Table 4. Two patients (12.5%) with candidemia (1 with *Candida albicans* and 1 with *Candida parapsilosis*) had a global response of failure at EOIVT; both had a microbiologic response of persistence at EOIVT (Table 5).

TABLE 1. Study Treatment Durations and Baseline Characteristics

Study treatment durations (safety population)	1 month–<2 years
Anidulafungin treatment	n = 19
Median duration, d (range)	13.0 (4–30)
Fluconazole treatment	n = 6
Median duration, d (range)	9.5 (3–15)
Total treatment duration (anidulafungin and fluconazole)	n = 19
Median duration, d (range)	16.0 (4–38)
Site of infection (MITT population),* n (%)	16 (100)
Blood	15 (93.8)
Catheter site	11 (68.8)
Abdominal	1 (6.3)
Feces	1 (6.3)
Urinary tract	1 (6.3)
Risk factors for candidemia (MITT population), n (%)	16 (100)
Use of broad-spectrum antibiotics	16 (100)
Use of central venous catheter	12 (75.0)
Total parenteral nutrition	9 (56.3)
Surgery	8 (50.0)
Abdominal surgery	7 (43.8)
Length of ICU stay ≥4 days	7 (43.8)
Mechanical ventilation	6 (37.5)
Use of systemic steroids or other immunosuppressives	6 (37.5)
Neutropenia	4 (25.0)
Chemotherapy	3 (18.8)
Solid-organ transplant	1 (6.3)
Other†	3 (18.8)

*Patients may have >1 site of infection.

†Other risk factors include the following conditions, as reported by the investigator: gastrostomy, head injury, short bowel syndrome, immunosuppression secondary to severe burns, stem cell transplantation, neoplasia, and desnutrition.

ICU indicates intensive care unit; MITT, modified intent-to-treat; n, number of patients in a specified category.

No patients relapsed or experienced new infection, and 15 of 16 (93.8%) achieved negative blood cultures. The median time to the first negative blood culture was 3 days. No resistance to anidulafungin was observed for Candida species.

Table 2 summarizes anidulafungin PK parameters from the 6 patients included in the PK substudy (age range: 0.1–1.8 years). In addition, plasma concentration of PS80 measured in 28 samples from 8 patients was found to be below the limit of quantification (5 µg/mL) for all samples, except one. A 20-month-old boy with a medical history of increased alanine transaminase and aspartate transaminase had a single PS80 concentration of 5.3 µg/mL, collected 1-hour postloading dose on day 1.

DISCUSSION

We report, to our knowledge, the first comprehensive prospective study of safety, efficacy and PK of anidulafungin in patients 1 month to <2 years of age. Anidulafungin was generally well tolerated in children with IC, or at high risk for IC, at a 3.0 mg/kg loading dose followed by 1.5 mg/kg daily.

Most TEAEs were expected adverse drug reactions or were associated with underlying conditions. TEAEs in patients 1 month to <2 years of age were largely similar to the overall population, although anemia was more commonly reported.[4] Events of anemia were mild-to-moderate in severity and resolved and were not considered treatment related but generally related to the patients' underlying conditions. No new safety concerns for anidulafungin were identified in patients 1 month to ≤2 years of age.

TABLE 2. Key Results in Patients With IC 1 Month to <2 Years of Age Who Received Anidulafungin

Baseline pathogen species* (MITT population), n (%)	1 month–<2 years, 16 (100)
Candida albicans	7 (43.8)
C. parapsilosis	5 (31.3)
C. tropicalis	2 (12.5)
C. glabrata	1 (6.3)
Candida species unspecified	1 (6.3)
Incidence of TEAEs affecting >20% of the safety population† AE, n (%)	19 (100)
Anemia	5 (26.3)
Diarrhea	4 (21.1)
Pyrexia	4 (21.1)
Vomiting	4 (21.1)
Anidulafungin global response success rate (MITT population), n (%)	16 (100)
EOIVT	11 (68.8)
EOT	11 (68.8)
Week 2 follow-up	11 (68.8)
Week 6 follow-up	11 (68.8)

Anidulafungin PK parameters of PK substudy population (6 patients)

	AUC_{24} (mg·h/L)‡	C_{max} (mg/L)§	T_{max} (h)	T_{last} (h)
Geometric mean (% CV)	66.4 (28)	5.96 (29)	N/A	N/A
Median (range)	70.2 (42.9–87.7)	6.77 (3.91–7.72)	0.39 (0.17–2.25)	24.0 (23.7–24.4)

*As identified by local microbiology laboratory (patients could have multiple *Candida* species at baseline).

†Includes AEs occurring up to 30 days after the last dose of the study treatment.

‡AUC_{24} was calculated based on the observed concentration data using the trapezoidal rule without any extrapolation. Where T_{last} is not equal to 24 hours, the actual AUC_{24} would be slightly higher or lower than the reported value.

§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.

AE indicates adverse event; AUC_{24}, area under the plasma concentration–time profile from time 0 to 24 hours; C_{max}, maximum observed concentration; EOT, end of treatment; MITT, modified intent-to-treat; n, number of patients in specified category; N/A, not applicable; T_{last}, time of last quantifiable concentration; T_{max}, time to C_{max}.

TABLE 3. Incidence of Treatment-Emergent Adverse Events of All Causalities (Affecting >5% and ≤20% of Safety Population)

AE, n (%)	1 Month–<2 Years, 19 (100)
Alanine aminotransferase increased	2 (10.5)
Aspartate aminotransferase increased	2 (10.5)
Bacteraemia	2 (10.5)
Pancytopenia	2 (10.5)
Rash	2 (10.5)
Sepsis	2 (10.5)
Thrombocytopenia	2 (10.5)
Device-related infection	1 (5.3)
Epistaxis	1 (5.3)
Febrile neutropenia	1 (5.3)
Hypocalcemia	1 (5.3)
Hypoglycemia	1 (5.3)
Leukopenia	1 (5.3)
Lower respiratory tract infection	1 (5.3)
Neutropenia	1 (5.3)
Pneumonia	1 (5.3)
Seizure	1 (5.3)
Thrombocytosis	1 (5.3)
Transaminases increased	1 (5.3)
Upper respiratory tract infection	1 (5.3)

Includes AEs occurring up to 30 days after the last dose of study treatment.
AE indicates adverse event.

TABLE 4. Anidulafungin Response Success Rates by Site of Infection and Neutrophil Count at EOIVT (MITT Population)

Proportion of patients, n/N (%)	1 Month–<2 Years, 16 (100)
Response by site of infection	
Blood only	9/14 (64.3)
Blood and other sterile sites*	1/1 (100)
Sterile site*	1/1 (100)
Response by neutrophil count	
≤500/mm^3	2/2 (100)
>500/mm^3	8/11 (72.7)

The global response of failure from a prior visit is carried forward.

*Other sites of infection included catheter sites (with absence of blood as site of infection), abdominal, urinary tract, feces. "Blood and other sterile sites" included 1 patient with blood, feces and urinary tract as sites of infection, and "Sterile site" included 1 patient with abdominal as site of infection.

MITT indicates modified intent-to-treat; N, total number of patients in specified category; n, proportion of patients achieving microbiologic or global response.

TABLE 5. Anidulafungin Response Success Rates (EOIVT) According to Baseline Pathogen (MITT Population)

	1 Month–<2 Years	
Baseline pathogen,* n/N (%)	Successful Microbiologic Response†	Successful Global Response‡
Candida albicans	5/7 (71.4)	4/7 (57.1)
C. parapsilosis	4/5 (80.0)	3/5 (60.0)
C. tropicalis	2/2 (100)	2/2 (100)
C. glabrata	1/1 (100)	1/1 (100)
Candida spp. unspecified	1/1 (100)	1/1 (100)

*As per local laboratory data.

†Includes eradication and presumed eradication.

‡Global response was programmed as a combination of clinical and microbiologic response. Global response of success was defined as clinical cure or improvement and microbiologic eradication or presumed eradication.

MITT indicates modified intent-to-treat; N, total number of patients with baseline pathogen identified; n, proportion of patients achieving microbiologic or global response.

No deaths were considered related to anidulafungin. All-cause mortality here was lower than previously reported for pediatric patients with IC mainly receiving amphotericin B as initial therapy (up to 24%).[5]

The proportion of patients 1 month to <2 years of age who experienced a global response of success at EOIVT (68.8%) was similar to findings in patients 2 to <18 years of age enrolled within the same study,[4] as well as to that observed in adults (75.6%).[6]

Furthermore, results for anidulafungin exposure in this study were comparable to the reported range of steady-state population PK parameters in adults with fungal infections receiving the standard anidulafungin dose (200 mg loading dose followed by 100 mg maintenance dose): steady-state area under the plasma concentration curve 110.3 mg·h/L (32.5 % CV) and steady-state maximum observed concentration 7.2 mg/L (23.3 % CV).[3] These findings are consistent with a previous PK study in which a loading dose of 3.0 mg/kg and daily maintenance dose of 1.5 mg/kg resulted in similar anidulafungin exposures in neonates and infants <2 years of age.[7]

PS80 exposure was investigated due to a lack of published excipient data in infants, and previous reports of possible hepatotoxicity in neonates and infants associated with other IV drugs formulated with PS80.[8,9] This study is, to our knowledge, the first to evaluate PS80 levels in infants. No hepatotoxicity or PS80 accumulation was detected, and the 1 patient who had a single PS80 concentration above the lower limit of quantification following the loading dose had a medical history of hepatobiliary events. The overall PS80 and anidulafungin PK findings further support anidulafungin use at the studied dose in pediatric patients >1 month of age.

The overall sample size of this study was small, and results should be interpreted with caution. A further limitation was the open-label, noncomparative study design, although this design is common in pediatric studies.[10]

Taken together, the data support the use of anidulafungin 3.0 mg/kg loading dose on day 1, followed by 1.5 mg/kg daily for the treatment of IC, including candidemia, in patients 1 month to <2 years of age.

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Current Abstracts

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Bracing for the Worst—Range Expansion of the Lone Star Tick in the Northeastern United States

Molaei G, Little EAH, Williams SC, et al. *N Engl J Med*. 2019;381: 2189–2192

Ticks and tickborne diseases are increasingly a major health concern for humans, domesticated animals and livestock. Reported cases of bacterial and protozoan tickborne disease doubled in the United States between 2004 and 2016. More than 90% of the nearly 60,000 cases of nationally notifiable vectorborne diseases reported in 2017 were linked to ticks. As the geographic ranges of multiple tick species are being discovered, new tickborne pathogens are emerging, and coinfections in ticks are surging. Rising global temperatures, ecologic changes, reforestation and increases in commerce and travel are all important underlying factors influencing the rate and extent of range expansion for ticks and tickborne pathogens.

Lone star (*Amblyomma americanum*) ticks of all life stages (larva, nymph and adult) feed predominantly on large mammals, especially whitetailed deer. Larvae and nymphs also feed on birds. The resurgence of lone star ticks is linked to increased populations of deer, eastern coyotes and wild turkeys. Lone star ticks have been established in the southeastern United States for well over a century; southern New Jersey was historically recognized as their northern range limit. Some reports of lone star ticks in the northeastern United States and more recently in eastern Canada may not necessarily reflect established breeding populations. In the past few decades, however, documented breeding populations have expanded into some parts of the Northeast.

Current environmental and climatic conditions favor the establishment and expansion of lone star ticks along the southern New England coast. Although the northward range expansion of the lone star tick is consistent with climate change, a recent study revealed that tick populations in New York are genetically distinct from those occupying the species' historical range. This finding suggests the possibility of adaptive evolution causing or coinciding with this range expansion and probably favoring pathogen transmission.

Field studies indicate that the lone star tick establishes populations in habitats with specific humidity ranges and that tick abundance is associated with the presence of invasive plants. Areas colonized by invasive plants are frequented by white-tailed deer, a prominent tick host and pathogen reservoir. Lone star ticks will traverse long distances when searching for a mammalian host, thereby accelerating their establishment in new areas.

Previously considered aggressive nuisance pests, lone star ticks have now been associated with several human diseases and medical conditions, including tularemia, ehrlichiosis, rickettsiosis, Heartland virus disease, southern tick-associated rash illness and red meat allergy (alpha-gal syndrome), and are probably also associated with Bourbon virus disease.

Most reports of lone star ticks in the northeastern United States come from tick submissions by the public to passive surveillance programs, which serve as an early warning system. Active surveillance is important for accurate determination of the extent of the northern range expansion of this vector, however. To be effective, active surveillance should be designed specifically for lone star ticks and should include targeting of areas with emerging populations identified by passive surveillance.

Comment: Abundant reproductive hosts, an increasingly hospitable climate, and genetic plasticity of the lone star tick support the continued invasion and establishment of this tick in the Northeast. Increasing population densities and subsequent range expansion, in conjunction with nondiscriminating biting habits and the capacity to transmit diverse pathogens, position the lone star tick as an important emerging health threat to humans, domesticated animals and wildlife. It is also plausible that the lone star tick will displace local tick species, transmit different pathogens than those species, and alter the tickborne disease landscape. A heightened awareness of the health risks associated with emergent tick vectors such as the lone star tick and their potential for changing the dynamics of tickborne diseases is warranted.