30 April 2020
EMA/304231/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ECALTA

International non-proprietary name: anidulafungin

Procedure No. EMEA/H/C/000788/II/0040

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC0-24,ss	area under the curve over a 24-hour dosing interval at steady state
AUC24	area under the curve over the 24-hour dosing interval
CL	clearance
C_{max}	maximum plasma concentration
$C_{min,ss}$	trough (minimum) concentration at steady state
CSR	clinical study report
EOIVT	end of intravenous treatment
EOT	end of treatment
EU	European Union
GI	gastrointestinal
IC	invasive candidiasis
ICC	invasive candidiasis, including candidemia
IIR	Investigator-Initiated Research
IV	intravenous
LD	loading dose
LFT	liver function test
LLOQ	lower limit of quantification
MD	maintenance dose
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MITT	Modified Intent-to-Treat
PD	pharmacodynamic(s)
PDCO	Paediatric Commission of the European Medicines Agency
PICU	paediatric intensive care unit
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PMAR	population modeling analysis report
PP	Per-Protocol
PS80	polysorbate 80
PT	preferred term
QD	once daily
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SD	standard deviation
SMQ	standard MedDRA query
spp.	species (plural)
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
Tmax	time to Cmax
Tlast	time of last quantifiable concentration
Vc	central volume of distribution
Vp	peripheral volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 18 March 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of the approved indication "treatment of invasive candidiasis (ICC)" to include paediatric patients aged from 1 month to less than 18 years of age; consequently, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated in order to add paediatric dosing instructions, warnings and precautions, clinical, and non-clinical information. The Package Leaflet is updated accordingly consequent to the revisions to the SmPC. In addition, the Marketing Authorisation Holder (MAH) has taken the opportunity to update the information in the SmPC and Package Leaflet in line with the current excipient's guideline for fructose.
The RMP Version number 13.0 dated 08 March 2019 which includes GVP module V rev 2 changes has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0053/2017) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0053/2017 was completed. The PDCO issued an opinion on compliance for the PIP P/0053/2017.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	18 March 2019
Start of procedure:	22 June 2019
CHMP Rapporteur Assessment Report	19 August 2019
PRAC Rapporteur Assessment Report	19 August 2019
PRAC members comments	28 August 2019
PRAC Outcome	5 September 2019
CHMP members comments	9 September 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 September 2019
Request for supplementary information (RSI)	19 September 2019
PRAC Rapporteur Assessment Report	10 January 2020
PRAC members comments	8 January 2020
CHMP Rapporteur Assessment Report	10 January 2020
PRAC Outcome	16 January 2020
CHMP members comments	20 January 2020
Updated CHMP Rapporteur Assessment Report	24 January 2020
Request for supplementary information (RSI)	30 January 2020
PRAC Rapporteur Assessment Report	6 April 2020
CHMP Rapporteur Assessment Report	15 April 2020
CHMP members comments	20 April 2020
Updated CHMP Rapporteur Assessment Report	23 April 2020
Opinion	30 April 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Anidulafungin is intended to treat invasive candidiasis.

State the claimed the therapeutic indication

Treatment of invasive candidiasis in adults and paediatric patients aged 1 month to <18 years.

Epidemiology and risk factors, screening tools/prevention

The overall incidence of candidemia in population-based studies ranges from 1 to 17.5 cases per 100,000 persons [source: UpToDate]. Candidemia is the leading cause of invasive fungal infections in hospitalized children. Among the different populations of paediatric patients, the highest rates of candidemia have been recorded in neonates and infants <1 year of age. In a study from the United States, the annual incidence of candidemia in infants was 15.7 - 17.5 per 100,000 whilst the incidence in children aged 1 to 19 years was 1 per 100,000 [J Paediatric Infect Dis Soc. 2018;7(3):e78]. Immunosuppressed children, children in intensive care units, children with central venous catheters, and neonates are most at risk for the development of candidemia. Risk factors include the presence of a central venous catheter, mechanical ventilation, damage to the intestinal mucosa, use of broad-spectrum antibiotics, use of parenteral nutrition.

Clinical presentation

The clinical manifestations of candidemia and invasive candidiasis vary from minimal fever to a fulminant sepsis with multi-organ system failure that is indistinguishable from severe bacterial infection.

Management

Currently, the following antifungal agents have an indication of treatment of invasive candidiasis in children: caspofungin, micafungin, amphotericin B and fluconazole. Voriconazole is licensed for treatment of candidaemia in children aged 2 and older.

According to the ESCMID guidelines [Clin Microbiol Infect. 2012 Dec; 18 Suppl 7():38-52.], echinocandins (i.e. caspofungin with a loading dose of 70 mg/m^2, followed by 50 mg/m^2/day, 2-4 mg/kg/day micafungin) are the alternative agents for the treatment of invasive candidiasis in children. These guidelines also recommend anidulafungin with a loading dose of 3 mg/kg, followed by 1.5 mg/kg/day. Note that caspofungin and micafungin are approved for paediatric patients, while anidulafungin is assigned for IC treatment in adult patients.

Fluconazole is only recommended in non-neutropenic patients who are not critically ill and have no prior azole exposure. Triazoles should be considered for hemodynamically stable patients in institutions with a

low incidence of less susceptible *Candida* spp. Voriconazole is recommended for invasive candidiasis as it shows more potency than fluconazole, especially in infections caused by *C. glabrata* and *C. krusei*.

2.1.2. About the product

Anidulafungin (PF-03910960) is a member of the echinocandin class of antifungals and exhibits fungicidal activity against *Candida spp.*

Anidulafungin was approved in Europe on 20 September 2007 and, at the time of this variation application, it was indicated for the treatment of invasive candidiasis (IC) in adults, with a recommended dose of 100 mg daily following an initial LD of 200 mg. As of 31 December 2018, IV anidulafungin had been approved in 96 countries worldwide and was marketed in 81 countries.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

No scientific advice has been given.

A preliminary assessment of this study was performed during a recent art 46 procedure (EMA/H/000788/P46/046), which was also submitted as part of another post-authorisation measure (Follow Up Measure 021). At the time, the MAH indicated that a variation application consisting of the full relevant data package (i.e. containing PK/PD data from several studies) was to be submitted by 2019.

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Non-clinical aspects

2.2.1. Introduction

The key nonclinical data relevant to paediatric development are:

- Assessment of anidulafungin antifungal activity in the following nonclinical models thought to be relevant to the question of dosing in neonates: disseminated candidiasis in rabbits, hematogenous Candida meningoencephalitis (HCME) model in rabbits, and endophthalmitis model in rabbits.
- Single-dose exploratory and definitive repeat-dose toxicity studies with subcutaneous administration anidulafungin in neonatal and juvenile rats.
- A risk assessment of polysorbate 80 as an excipient in anidulafungin in the treatment of neonates.
- A literature search and review of published nonclinical safety information has also been conducted. Findings from all nonclinical studies were reviewed for their potential impact on patient safety. The safety and efficacy of anidulafungin are well documented in over 10 years of clinical use, and the newly-presented nonclinical studies do not affect the benefit: risk profile of anidulafungin for its indicated clinical use.

2.2.2. Pharmacology

Disseminated candidiasis in rabbits (Petraitiene et al., 1999)

This study evaluated the efficacy of anidulafungin (aka LY303366) compared to amphotericin B, and fluconazole in a persistently neutropenic rabbit model of disseminated candidiasis (Candida albicans). Anidulafungin doses were 0.1, 0.25, 0.5, and 1.0 mg/kg per day. Fungal burden was assessed in liver, spleen, kidney, lung, vena cava, and brain. Doses of anidulafungin ≥0.5 mg/kg cleared fungal burden in all tissues to below lower limits of detection. Doses of 0.25 mg/kg produced a significant reduction in fungal burden in all tissues with the exception of the brain. The PK of anidulafungin was determined in healthy rabbits at the same doses. Although the absolute AUC values would not be considered directly translatable to humans, given the nature of this experimental model (neutropenic animals, etc.), it is noted that the PK was linear, i.e., doses were directly proportional to AUC.

Overall, these data suggest that anidulafungin can penetrate brain tissue and produce antifungal activity, although 2x higher doses were needed to produce a significant decrease in fungal burden in the brain relative to other tissues. It should also be noted that activity of anidulafungin in brain tissue in this study should be considered in light of the animals having disseminated disease, and hence the blood-brain barrier would be expected to be disrupted relative to a healthy animal.

HCME model in rabbits (Warn et al., 2012)

This study was conducted specifically to address the question of appropriate dosing of anidulafungin in neonates. A rabbit model of HCME was used to define PK/PD relationships for antifungal activity of anidulafungin in the brain, and subsequently, a population PK model for human neonates was used to project efficacious dosing regimens, based on the observed PK/PD in rabbit HCME.

Rabbits were inoculated with C. albicans intravenously, after which there was progressive logarithmic growth in the cerebrum. Without therapy, no animals survived beyond 96 hours. Anidulafungin (5, 10, or 20 mg/kg) was administered starting 48 hours after inoculation. An antifungal effect as measured by fungal burden in the cerebrum was evident at the 10 and 20 mg/kg doses, while a smaller effect was observed at the 5 mg/kg dose. PK of anidulafungin was linear, with dose-dependent penetration into the cerebrum. Based on PK/PD bridging to human neonates, it was estimated that the AUC of 100 to 120 mg*h/L that is associated with clinical efficacy in adults would be associated with a submaximal antifungal effect, and that an AUC of approximately 200 to 240 mg*h/L should be targeted.

One limitation of this study is that fungal burden in non-CNS tissues was not reported, and hence it was not possible to assess the relative dose/exposures to treat CNS tissues versus non CNS. That limitation was addressed however in a subsequent publication, as described below.

Experimental Candida Endophthalmitis model in rabbits (Livermore et al., 2013)

This publication is derived from the same HCME rabbit study described above. However, this publication reports the fungal burden and antifungal activity of anidulafungin in the vitreous humor and the kidney, whereas the prior publication was focused on the brain.

Rabbits were inoculated with C. albicans intravenously, after which there was progressive logarithmic growth in the vitreous humor and the kidney. Anidulafungin (5, 10, or 20 mg/kg) was administered starting 48 hours after inoculation. The 5 mg/kg dose of anidulafungin had minimal effect on fungal burden in the vitreous humor, but did have an effect on the kidney. The 10 and 20 mg/kg doses had progressively greater effects in both tissues, with effects in the kidney more pronounced than vitreous humor. It was estimated that stasis is achieved in the kidney at a plasma AUC of approximately 100

mg*h/L, whereas stasis in the vitreous humor was achieved at a plasma AUC of approximately 270 mg*h/L.

Overall, the results of these two publications using the rabbit HCME model suggest that an approximately 2- to 3-x higher dose/exposure of anidulafungin is needed to treat infections of the brain and vitreous humor relative to the kidney. This is likely because both brain and vitreous humor are protected by blood/brain (or blood/ocular) barriers, as opposed to the kidney, which is well-perfused.

2.2.3. Pharmacokinetics

As part of the development of the paediatric indication for anidulafungin, the tissue distribution of anidulafungin into bone, brain and heart tissues of neonatal rats (postnatal Day 4 to 8) was characterized. After repeat dose administration, concentrations of anidulafungin in bone were similar to plasma, and concentrations of anidulafungin in the heart were 1.3- to 1.8-times higher than plasma. Concentrations of anidulafungin in the brain were lower than plasma after a single dose, but concentrations were higher after 24 hours and were similar to levels in plasma after 5 days of dosing. Results from this study demonstrated that anidulafungin distributes to bone, brain and heart tissues following single- or repeat-dose subcutaneous administration to neonatal rats.

2.2.4. Toxicology

Juvenile studies

Single-dose, exploratory and definitive repeat-dose toxicity studies with subcutaneous administration were conducted with anidulafungin in neonatal rats and in combination with voriconazole in juvenile rats.

Anidulafungin was evaluated in a dose-range single-dose toxicity study in neonatal rats at 0, 75, and 100 mg/kg/day. Doses up to 100 mg/kg were well tolerated in rat pups administered anidulafungin intravenously, subcutaneously, or intraperitoneally on postnatal Day (PND) 7. At 100 mg/kg, lower body weight gains were observed 24 hours after dosing on PND 7 in each sex that was administered anidulafungin intravenously. Despite the body weight gains at each tabulated interval, there was no overall change in body weight at the end of the recovery period. All single doses of anidulafungin appeared well tolerated. Toxicokinetic data suggested the plasma concentration-time profile after subcutaneous dosing is most consistent with the clinical plasma concentration versus time profile.

In the repeat-dose neonatal and juvenile rat studies, rats were administered anidulafungin subcutaneously alone or in combination with voriconazole (oral gavage). In neonatal studies, rats were administered anidulafungin (SC; 0, 3, 10, or 30 mg/kg/day) from PND 4 to 62, with a 5-week recovery period. In juvenile studies, rats received anidulafungin (SC; 30 mg/kg/day) or voriconazole (PO; 3 or 10 mg/kg/day) alone or in combination once daily from PND 21 to 56 with a recovery period to PND 84. The primary anidulafungin-related effects were reduced body weights (including terminal weights) and body weight gains, increased liver weights, hepatocellular single cell necrosis (in the juvenile definitive study only) and minimal changes in hematology and serum chemistry parameters. These effects were consistent with findings that occurred in previous studies with multiple species evaluating the test article and were not considered adverse because of the small magnitude of change and lack of correlation with microscopic changes. Furthermore, the addition of voriconazole to anidulafungin treatment did not result in new toxicity when administered for 5 weeks at combined dosages as high as 10/30 mg/kg/day (voriconazole/anidulafungin). The NOAEL for anidulafungin in the neonatal rat definitive repeat-dose study following once-daily subcutaneous administration was 30 mg/kg/day.

Other toxicity studies

Risk Assessment for Polysorbate 80

Anidulafungin is formulated as a sterile, lyophilized product for intravenous infusion that contains approximately 25% polysorbate 80 at a ratio of 2.56:1 polysorbate 80: anidulafungin (mg:mg). Polysorbate 80 has been used extensively as a solubilizing agent in other marketed parenteral drug products. A review of safety data pertaining to its use in neonates was performed to determine if the increased anidulafungin doses needed to treat neonates with invasive candidiasis with central nervous system involvement and the consequent higher exposures to polysorbate 80 are appropriate for this patient population. This review is summarized below.

Anidulafungin has been administered to neonates using the commercial, polysorbate 80 containing formulation in a completed Phase 1 study, and was generally well-tolerated at the dose and duration that was used in the trial. However, the increased doses of anidulafungin and hence polysorbate 80 under consideration for use in neonates are 2- and 3-fold greater than the dose used in the completed study, and could potentially be administered for a longer duration. The proposed mean daily dose of polysorbate 80 that would occur at the highest dose of anidulafungin under consideration is similar to doses that are administered to neonates receiving approved parenteral vitamin preparations. The cumulative polysorbate 80 doses that would occur at the highest dose of anidulafungin under consideration are approximately 8.7-fold lower than the lowest cumulative precedent intravenous dose, and approximately 12-fold lower than the mean precedent cumulative dose of polysorbates at which neonatal mortality occurred following E-Ferol administration. While these comparisons indicate that a safety margin exists, it should be noted that in the case of E-Ferol the calculated margins are based on polysorbate doses that were associated with severe toxicity and deaths. In addition, anidulafungin itself has been shown to produce hepatic toxicity at low multiples of human exposure in nonclinical studies in rats and monkeys, and the doses to be administered in the planned clinical study are predicted to result in anidulafungin exposures similar to those observed at the NOAEL. Importantly, there is uncertainty about the role of polysorbates in the toxicity and deaths in neonates that received E-Ferol. Regardless, there are currently insufficient preclinical and clinical safety data available to definitively support the use of the proposed increased concentrations of polysorbate 80 in neonates at higher anidulafungin doses.

2.2.5. Ecotoxicity/environmental risk assessment

No updated environmental risk assessment was submitted by the MAH.

2.2.6. Discussion on non-clinical aspects

The efficacy of anidulafungin for infections of the brain has been evaluated in two rabbit disease models, a neutropenic model of disseminated disease and a hematogenous Candida meningoencephalitis (HCME) model. These models appear relevant for a neonatal population due to a higher likelihood of disseminated disease, including the possibility of infection within the central nervous system. The rabbit models show that it is likely that a 2 to 3-fold higher plasma concentration of anidulafungin is required to treat fungal infections that may involve CNS tissues. There are, however, no clinical data to support a higher dose, since all patients in the clinical trials received a dose resulting in AUC values similar to those in adults. Higher doses are therefore not recommended.

In neonatal rats, anidulafungin distributes to the brain, with similar concentrations to plasma after 5 days of dosing.

Repeated dose toxicity studies in neonatal (dosing from PND4) or juvenile (dosing from PND21) rats revealed no increased susceptibility to liver toxicity as observed with adult animals. Also, no new toxicities were observed with doses up to 30 mg/kg/day.

High plasma concentration of polysorbate 80, an excipient present in the Ecalta formulation, is associated with severe neonatal toxicity, including death. Higher doses of Ecalta which would be needed to treat CNS infection would result in higher polysorbate 80 concentrations. A higher dose, however, is not applied for in the current procedure. There are currently insufficient preclinical and clinical safety data available to definitively support a higher dose than the one recommended in the SmPC (3.0 mg/kg loading dose, followed by 1.5 mg/kg/day maintenance). An appropriate warning is present in SmPC section 4.4.

It was considered that a phase II ERA is already present in the dossier. For this ERA in the dossier, a default Fpen has been used to come to a PECsurfacewater of 1.0 µg/L, triggering a phase II assessment. In phase II, the PEC was revised based on human transformation data, and risk assessment for the different compartments were made using study data. It was therefore accepted that addition of a paediatric population to the indication will not alter the ERA, as a default Fpen was used.

2.2.7. Conclusion on the non-clinical aspects

Repeated dose toxicity studies in neonatal or juvenile rats revealed no increased susceptibility to liver toxicity as observed with adult animals.

High plasma concentration of polysorbate 80, an excipient present in the Ecalta formulation, is associated with severe neonatal toxicity, including death. Higher doses of Ecalta, which would be needed to treat CNS infection, would result in higher polysorbate 80 concentrations. This is not relevant, however, as a higher dose is not applied for with this procedure.

Based on the information submitted during the assessment of this application, the new/extended indication may lead to a significant increase in environmental exposure of anidulafungin. It was however accepted that addition of a paediatric population to the indication will not result in the need to alter the ERA.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

The MAH submitted data from two clinical studies and a population PK/pharmacodynamic (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

- A8851008 - A Prospective, Open-Label Study to Assess the Pharmacokinetics, Safety and Efficacy of Anidulafungin when used to Treat Children with Invasive Candidiasis, including Candidemia

Duke University Investigator-Initiated Research Study (Duke IIR Study)

The Duke IIR Study was an investigator-initiated study conducted at Duke University in the United States (US). It was an open-label study designed to assess the safety, tolerance, and pharmacokinetics of IV anidulafungin administered to infants and neonates at risk for ICC.

Study design

The Duke IIR Study was a prospective, open-label, single-centre, 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 CHMP considered the design of the pharmacokinetic part of the study to be acceptable.

Bioanalytical methods

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%.

A validated bioanalytical method for the analysis of anidulafungin in plasma was applied, the accuracy and precision of which were acceptable to the CHMP.

Results

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. One hundred and nineteen plasma concentrations were obtained from 14 subjects.

According to the MAH, anidulafungin concentration-time profiles were similar between age cohorts. Pharmacokinetic parameters (noncompartmental analysis) after the loading dose and multiple dosing are

summarized in table PK 1. After the loading dose, only observed maximum anidulafungin concentrations were obtained; other PK parameters were not calculated for the loading dose given an insufficient number of samples.

Table PK 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

AUCss: Area under the plasma concentration-time curve over 24-hour dosing interval at steady state; CL: Clearance; Cmax: Maximum plasma concentration; Cmax LD: Maximum plasma concentration after the loading dose; CV% Coefficient of variation; VSS: Volume of distribution at steady state; N: number of subject contributing to the summary statistics.

Conclusion

Anidulafungin plasma concentration-time profiles were similar between age cohorts. Exposure to anidulafungin was not related to postmenstrual age. The overall anidulafungin exposure in infants and neonates administered 1.5 mg/kg/day of anidulafungin was similar (within 15%) to that of older children and adults (AUCss 100 µg*h/ml).

The combined exposure data of infants and neonates administered 1.5 mg/kg/day of anidulafungin (i.e. 93 µg.h/ml) was comparable to those observed in adults (100 µg.h/ml). However, in neonates, the exposure is about 27% lower and in infants the exposure is about 21% higher compared to adults. The CHMP noted that the results of this study should be interpreted with caution, considering the low number of subjects included and the observed variability up 66%. However, the data were included in the popPK analysis combined with data from study A8851008, including a higher number of subjects (n=60).

Study A8851008

Study design

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 paediatric patients 1 month to <18 years of age.

All study subjects received anidulafungin IV treatment (3.0 mg/kg loading dose on study day 1 followed by 1.5 mg/kg maintenance dose daily thereafter), administered at a rate of 1.1 mg/min or less. Subjects were to receive anidulafungin IV for a minimum of 10 days to a maximum of 35 days. There was an option to switch to oral treatment with fluconazole (6 to 12 mg/kg/day, maximum 800 mg/day) after at least 10 days of IV treatment, provided the subject met pre specified criteria.

- In order to confirm the appropriateness of the protocol's study dosing regimen for the 1 month to <2 years old age group, the first 6 children in this age group were enrolled in a PK sub-study in which intensive PK sampling was conducted at selected centers. The PK sub-study completed prior to protocol Amendment 8, therefore polysorbate 80 plasma concentrations were not assessed in these 6 subjects. 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

Blood samples (approximately 0.3 to 0.5 mL each) for anidulafungin measurement and blood samples (approximately 1 mL each for subjects enrolled under protocol amendment 8) for polysorbate 80 measurement were collected at 3 to 5 occasions at the same time points as anidulafungin during Day 1 through Day 9 for all study subjects, with the exception of subjects in the PK sub-study:

- 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)

The CHMP considered the design of the pharmacokinetic part of study A8851008 to be acceptable.

The doses of anidulafungin used in this study (3.0 mg/kg loading followed by 1.5 mg/kg/day) were expected to achieve total exposures comparable to those observed in a pivotal Phase 3, double-blind, randomized study (VER002-9) of subjects aged 16 years and above with ICC where anidulafungin was compared to fluconazole. Benjamin et al. demonstrated that paediatric body weight was the primary consideration in achieving anidulafungin plasma concentrations comparable to adults, and further showed that paediatric subjects receiving 1.5 mg/kg/day IV anidulafungin had concentration profiles and drug exposures similar to those in adults receiving 100 mg/day.

Bioanalytical methods

The plasma samples were analyzed for anidulafungin and polysorbate 80 using validated high performance liquid chromatography with tandem mass spectrometric method (HPLC-/MS/MS). The lower limit of quantification (LLOQ) for anidulafungin was 50.00 ng/ml. The LLOQ for polysorbate 80

was 5.00 µg/ml.Validated bioanalytical methods for the analysis of anidulafungin and polysorbate 80 in plasma were applied, the accuracy and precision of which made them acceptable to the CHMP.

Results

Pharmacokinetic sub-study

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. One subject [redacted] did not have a sample at the end of loading dose on Day 1.

The anidulafungin plasma concentrations for all 6 of the subjects are presented by subject and sampling time on Day 1 and 2. A descriptive summary of anidulafungin PK parameters from these 6 subjects is presented and summarized in table PK 2.

Table PK 2. 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.

It was concluded that the anidulafungin exposures in these 6 subjects fell within the expected range for adult ICC patients dosed with 200 mg load followed by 100 mg/day (110 µg.h/ml) (see also discussion on pharmacokinetics).

Pharmacokinetic sparse sampling

The PK dataset, excluding data from the 6 subjects enrolled in the PK sub-study, included 253 anidulafungin plasma concentrations from 60 subjects (11 subjects from 1 month to <2 years; 19 subjects 2 to <5 years; 30 subjects 5 to <18 years) who underwent sparse PK sampling. These data are presented for individual subjects by sampling time and age group and will be combined with the PK sub-study and additional concentration data from other studies and analyzed in a population PK analysis to be reported separately (see below). The anidulafungin plasma concentrations from these 60 subjects generally fell within the expected ranges for adult ICC subjects dosed with 200 mg loading followed by 100 mg per day.

Polysorbate 80

The final PK dataset contained 28 polysorbate 80 samples from 8 subjects (1 month to <2 years of age) enrolled under protocol amendment 8. These data are presented for individual subjects by sampling time and age group.

Only one subject of the 8 subjects had one sample which was collected 5 hours post infusion on Day 1 from subject [redacted], a [redacted] white male weighing 13 kg, was above the lower limit of quantitation (LLOQ: 5.0 µg/mL) with a polysorbate 80 concentration of 5.3 µg/ml. Otherwise, none of the other samples, including those for this subject, had detectable polysorbate 80 concentrations and they were all below the LLOQ. Therefore, plasma concentrations of polysorbate 80 were low or undetectable in infants 1 month to <2 years of age following administration of anidulafungin 3.0 mg/kg loading and 1.5 mg/kg per day.

Conclusions

Anidulafungin and polysorbate 80 PK results support an anidulafungin dose recommendation of 3.0 mg/kg load followed by 1.5 mg/kg/day for paediatric ICC patients aged 1 month to 17 years.

The finding of extremely low/undetectable levels of polysorbate 80 post-infusion, along with safety results from the study, suggest that presence of this excipient in the anidulafungin formulation, at the recommended dose of anidulafungin, is not a safety issue in infants as young as 1 month of age.

The above conclusions on the results of pharmacokinetic characterization were agreed upon by the CHMP.

Discussion on pharmacokinetics

The goal of the PK-sub study was to confirm the appropriateness of the dosing regimen for the 1 month to <2 years old age group. It was concluded that anidulafungin exposure in these 6 sub-study subjects fell within the expected range for the adult population, which would support the chosen dose regimen.

The Pharmacokinetics of anidulafungin have been characterized adequately during this study. The dosing regimen of 3.0 mg/kg loading, followed by 1.5 mg/kg maintenance in the population of 1 month to <2 years, resulted in a lower exposure to those observed in the adult population. An $AUC_{0\text{-}24}$ of 66.4 µg.hr/ml (28%CV) and C_{max} of 5.96 µg/ml (29%CV) was observed for the first 6 subjects in the 1 month to <2 year age group, while for the adult population (at a loading dose of 200 mg and a daily dose of 100 mg) AUC_{ss} was about 110 µg.h/ml and C_{max} 7.2 µg/ml. It is noted that the observed AUC is lower in the young age group, and the calculated AUC was not based on measurements from steady-state conditions. Population PK/PD analysis have been applied to support that exposure in the youngest age group compared to adult patients is in the same range and therefore support the appropriateness of the dosing regimen of 3.0 mg/kg loading followed by 1.5 mg/kg maintenance the next day (see section 5.3.4 PK/PK modelling).

Further based on this study, in which polysorbate 80 was measured 5-hour post-dose in samples from 8 subjects in the month to <2 years of age group, concentrations of polysorbate 80 are not expected to be higher than 5.3 µg/ml in these patients.

2.3.3. Pharmacodynamics

No new information on the pharmacodynamics of anidulafungin was submitted with this application. This is appropriate and acceptable.

2.3.4. PK/PD modelling

As recorded in the European Medicines Agency (EMA) communication of 24 September 2007 which summarized all the post-approval commitments agreed during the European review and approval of Ecalta, for follow-up measure (FUM) 018/018.1/018.2, the Sponsor committed to the incorporation of a PK/PD component in the following studies A8851008, A8851011 and A8851019 and the submission of the

results when available to explore the relationships between anidulafungin exposure and response in patients with ICC.

All 3 studies evaluated safety and efficacy in ICC patient populations (adult and paediatric). PK data were obtained in subsets of patients in studies A8851011 and A8851019.

Anidulafungin data in paediatric subjects under 2 years of age were limited in Study A8851008 due to enrollment challenges. To complement the data collected within this age group in the A8851008 study, the anidulafungin PK data (intensive PK) in infants and neonates with suspected serious infections from the Duke IIR Study were included in the PK analysis. Although the Duke IIR Study was excluded from the efficacy and safety analyses, since it was primarily designed as a Phase 1 PK study, with this addition, the PK profile of anidulafungin was characterized with the full span of the age range.

Pharmacokinetic-Pharmacodynamic analysis of anidulafungin in paediatric and adult patients with invasive fungal infections

A nonlinear mixed-effects modeling approach was used to describe PK across adult and paediatric subjects (0-18 years) with ICC. In this joint analysis, the anidulafungin exposures in the paediatric subjects are comparable to those in adult subjects.

Exploratory graphical exposure-efficacy (global response and all-cause mortality) analyses showed no relationship between anidulafungin exposure measures and efficacy endpoints at the end of IV treatment (EOIVT), end of treatment (EOT), and end of study (EOS). This is consistent with previous findings. Global response success rates of 63% or more were observed across the studies at EOIVT and EOT. Based on subjects with PK data, global response rates at EOIVT for Studies A8851008, A8851011, and A8851019 were 71%, 90.3%, and 70.7%, respectively.

Although there was an observed trend towards an increased incidence of hepatic adverse events (AEs) with higher exposures, no statistically significant associations between anidulafungin exposures and hepatic or gastrointestinal (GI) AEs were identified in this joint paediatric and adult analysis using either linear or maximum effect (Emax) relationships.

These findings are consistent with the previous exposure-safety analysis, in which no association between anidulafungin exposures and hepatic and GI AEs were identified in paediatric or adult subjects treated for ICC.

Study Design

Four studies were included in the PK analyses.

- Study A8851008.
- Study A8851011 was a 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. Subjects received anidulafungin IV treatment 200 mg LD followed by 100 mg MD for a minimum of 5 days. Sparse PK was to have been sampled in 33 subjects.
- Study A8851019 was a Phase 3b, prospective, open-label, non-comparative study for the treatment of documented ICC in intensive care unit adult patients (≥18 years). Subjects received anidulafungin IV treatment of 200 mg LD followed by 100 mg MD for a minimum of 10 days. Intensive PK was performed in 22 subjects with sparse PK in 28 subjects.
- The Duke IIR study.

PK sampling schedule for the 4 studies is presented in table PK 3.

Table PK 3. PK sampling schedules.

Study	PK Sampling Schedule
A8851008	See Section 2.7.2.2.2.1.2.
A8851011	Day 2 and Day 5: pre-dose, Day 3: post-dose (0-3 h following end of infusion), and Day 4: delayed post-dose (6-12 h following end of infusion)
A8851019	All patients in PK dataset (except 22 patients with intensive PK sampling[a]): Day 3 and Day 9: pre-dose, Day 5: post-dose (0-3 h following end of infusion), and Day 7: delayed post-dose (6-12 h following end of infusion)
Duke IIR Study	See Section 2.7.2.2.1.1.

[a] All PK samples were to be collected after at least 2 days of dosing with anidulafungin: pre-dose (prior to the start of infusion), and at 1.5, 2, 3, 4, 8, 12, and 24 hours after the start of infusion

The efficacy population consisted of modified intent-to-treat (mITT) patients (subjects with confirmed *Candida* infection who received at least one dose of study drug). The efficacy endpoints included global response (success versus [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. Only subjects with PK were included in the joint exposure-efficacy analysis.

The safety population consisted of all subjects who received at least one dose of the study treatment (anidulafungin). Two types of adverse events (AEs) (i.e., all-causality hepatic and GI AEs) were the focus of this analysis. Subjects who did not experience hepatic or GI AEs were considered as non-AE subjects. AEs that were reported by the investigator as related to study drug were considered as treatment-related AEs. Only subjects with PK were included in the joint exposure-safety analysis.

Note that the Duke IIR Study was not included for either exposure-efficacy or exposure safety analyses since it was designed as primarily as a PK study.

Methods

The population PK analyses were conducted using the nonlinear mixed-effects modeling approach. Exposure-response (efficacy and safety endpoints) modeling was performed using maximum likelihood method once graphical analyses demonstrated a possible exposure-response relationship. The software packages NONMEM, version 7.3 and Perl-speaks-NONMEM (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 for presentations and reports. The preferred estimation methods were first-order conditional estimation method with interaction (FOCEI) for PK and LAPLACE for categorical data (efficacy and safety).

The goodness of fit of different models to the data was evaluated using the following criteria: change in the objective function value (OFV), visual inspection of various diagnostic plots, the precision of the parameter estimates. Visual predictive check (VPC) and prediction corrected visual predictive check (pcVPC) were performed for the final PK model to qualify the models for prediction of the concentration data.

Exposure parameters at steady state AUC0-24,ss, Cmin,ss, and AUC0-24,ss/MIC for PK/PD analyses were calculated using the individual parameter estimates obtained from the final PK model.

Results

Observed PK Data

A total of 163 subjects (95 males and 68 females) from the 4 studies were included in the PK analysis, with 14 from the Duke IIR study, 66 from Study A8851008, as well as 33 and 50 subjects from study

A8851011 and study A8851019, respectively (see table PK 4). A total of 797 anidulafungin concentrations were included in the PK analysis, with 391 concentrations from paediatric subjects.

Table PK 4. Summary of number of subjects and PK samples and demographics in the PK analysis by study.

	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)

ePharmacology artifact ID RA15231258.
PK: pharmacokinetic; SD: standard deviation
[a] in Study A8851019, one [redacted] subject was missing Race information

Observed Efficacy Data

There were a total of 484 subjects (64 paediatric and 420 adults) in the mITT population from the 3 studies included in the efficacy data. Of these, 134 subjects had paired estimated exposure parameters (PK) and efficacy data available and were included in the analyses.

Only 121 subjects had MIC data available for anidulafungin PK/PD index assessment. In the paired PK/PD mITT population, global response of success rate at EOT was 72.58%, 83.87% and 68.29% for study A8851008, A8851011, and A8851019, respectively. The percentage of subjects in the joint analysis surviving at EOS was 88.71%, 96.77%, and 73.17% for studies A8851008, A8851011, and A8851019, respectively.

In study A8851008, there were 8 deaths during the study reporting period, and 2 deaths (subjects [redacted] and [redacted]) that occurred outside of the safety reporting period (after the 6-week follow-up visit) were included in all-cause mortality analysis as alive at EOS. There were 17 and 44 subjects who died by EOS for studies A8851011 and A8851019, respectively but not all had paired PK data.

Observed Safety Data

There were a total of 566 subjects in the safety population across all studies. However, only 149 of these subjects had estimated exposure parameters (PK). Subjects who did not experience either hepatic or GI AEs were counted as not having an AE (non-AE) as long as they had PK data.

In study A8851008, there were a total of 68 subjects included in the safety population. Of these, 66 subjects were included in exposure/safety analyses as 2 subjects (subject [redacted] and [redacted]) did not have PK taken. Thirty-two (48.48%) of the 66 subjects had neither hepatic nor GI AEs reported during the anidulafungin treatment period. Twelve (18.18%) subjects and 27 subjects (40.91%) reported

hepatic and/or GI AEs emergent during anidulafungin treatment, respectively. Of these, 6 and 7 subjects had treatment related hepatic and GI AEs during treatment period, respectively. There were 6 and 18 subjects who had more than one hepatic and GI AEs, respectively.

Thirty-three and 50 subjects had paired exposure and safety data available in studies A8851011 and A8851019, respectively. Of these, 26 (78.79%) and 31 (62%) had neither hepatic nor GI AEs, 3 (9.09%) and 7 (14%) had hepatic AEs, and 6 (18.18%) and 15 (30%) had GI AEs for Studies A8851011 and A8851019, respectively.

Population PK Modeling

The key runs for model development are listed in table PK 5. Based on the OFV change and diagnostic plots, Run15 was selected as the final base model.

Table PK 5. List of key runs.

Run No.	ePharm ID	Model Description	OFV	ΔOFV	Comment
Run1	AS711554	base model with WT as a structural covariate on CL (power function), Vc and Vp (linear relationship)	903.817		
Run2	AS711557	as run1, but standard allometric scaling for WT on Vc and Vp	903.817	0	
Run4	AS711563	as run2, adding a covariance term between the IIV in CL and Vc	857.812	-46.005	Keep in the model
Run15	AS711711	as run4, but estimating exponents for the WT effect on Vc and Vp	833.826	-23.986	BASE and FINAL MODEL
Run20	AS711745	as run15, testing age effect on CL	830.368	-3.458	not significant
Run21	AS711747	as run15, testing sex on CL	833.467	-0.359	not significant
Run22	AS711749	as run15, testing age effect on Vc	832.858	-0.968	not significant
Run23	AS711751	as run15, testing sex on Vc	833.802	-0.024	not significant

OFV: objective function value; CL: clearance; Vc: central volume of distribution.
Vp: peripheral volume of distribution; WT: body weight; IIV: inter-individual variance.

The final PK model was a two-compartment disposition model with first order elimination. Body weight was a structural covariate on clearance (CL), central volume of distribution (Vc), and peripheral volume of distribution (Vp). No other covariates (eg. age or sex) were identified as statistically significant. For a typical subject with a body weight of 70 kg, CL, Vc, Vp, and inter-compartmental clearance (Q) were estimated to be 1.16 L/h, 26.7 L, 22.4 L, and 2.37 L/h, respectively. The inter-individual variance (IIV)s for CL, Vc, Vp and Q were 37.9%, 46.5%, 53.8% and 52.2% respectively (see table PK 6 parameter estimates for the final model).

Table PK 6. Parameter estimates for the final 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

ePharmacology artifact ID RA15257448.
[a]The estimate is for a subject weighing 70 kg.
[b]Estimate of the covariance between CL and Vc.

The concentration data across the studies were adequately described by the final model (figure PK 1). There were no trends of CWRES vs TIME (time after the first dose) and PRED plots stratified by study. Distributions of IIVs are shown in figure PK 2.

Figure PK 1. Basic Goodness of Fit for the Final Model by study.

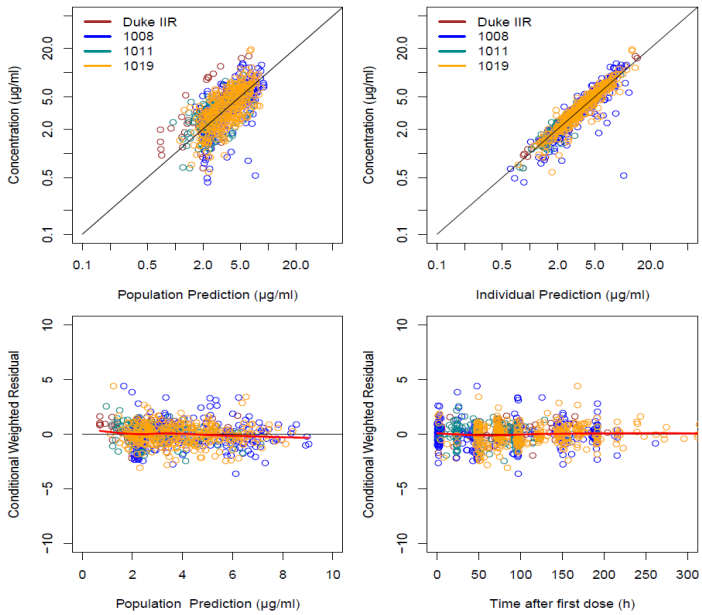
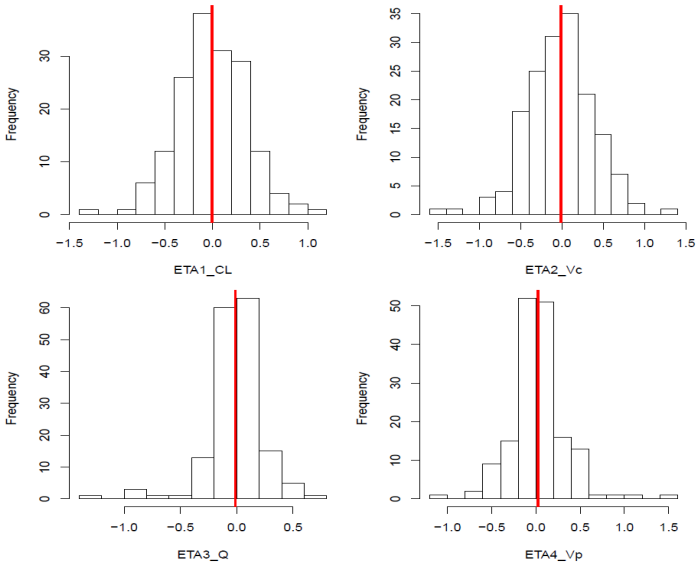
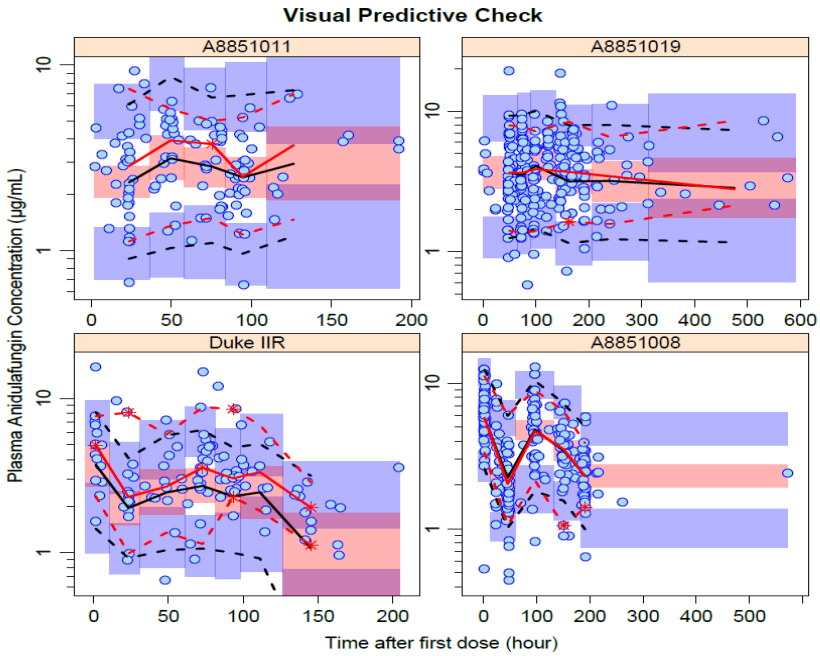


Figure PK 2. Histograms of ETAs.



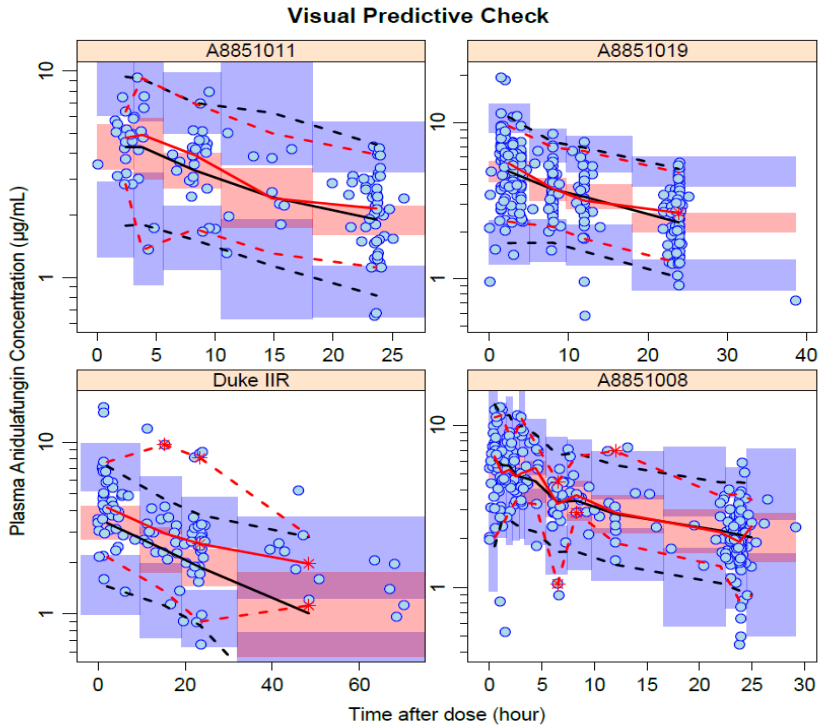
1000 simulations were performed for the final model (run15) to compare simulated data with the original data. The plots of VPC stratified by study versus time after first dose are presented in figure PK 3. Figure PK 4 is the VPC plots stratified by study versus time after dose. In general, the plots indicate that the final model predicts the data well across the studies, except where Duke IIR Study data were under-predicted. Further, pcVPC by age group is shown in figure PK 5. A good match is observed between the median, 5th and 95th percentiles for the observed and simulated data across the age group.

Figure PK 3. Visual Predictive Check stratified by study versus time after first dose for the Final Model (run15).



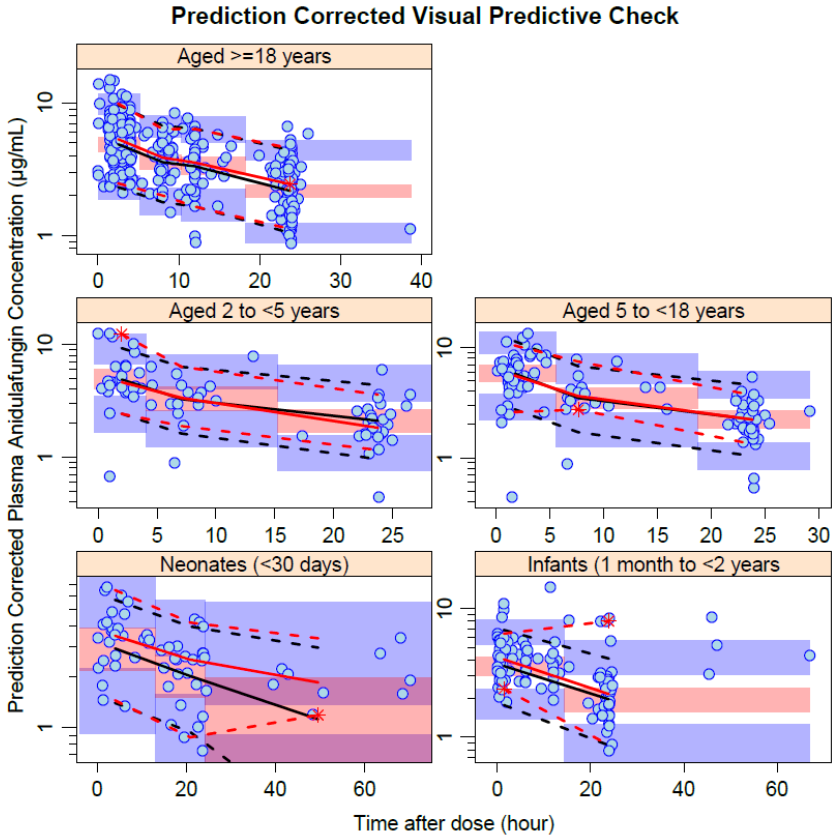
ePharmacology artifact ID RA14965861.
Red and black dashed lines present 90% confidence interval (CI) (95% upper limits and 5% lower limits) of observed and simulated data, respectively. Red and black solid lines are median (50%) of observed and simulated data, respectively. Blue dots are observed data. Shadow areas are 95% CI. PROT: protocol

Figure PK 4. Visual Predictive Check stratified by study and dose versus time after dose for the Final Model (run15).



ePharmacology artifact ID RA14966085.
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. PROT: protocol

Figure PK 5. Prediction Corrected Visual Predictive Check stratified by age group versus time after dose for the Final Model (run15).



ePharmacology artifact ID RA15386561.
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. PROT: protocol

Individual parameter estimates from the final PK model were used for estimation of anidulafungin exposures. The exposure and PK parameters (for maintenance doses) summarized by age groups are presented in table PK 6. Predicted anidulafungin exposure parameters for paediatric subjects in study A8851008 are summarized in table PK 7. In addition, the boxplots of AUC0-24,ss and Cmin,ss stratified by age groups are presented in figure PK 6 and figure PK7, respectively.

Table PK 6. Summary of estimated anidulafungin exposure and PK parameters in paediatric and adult subjects by age groups (doses (LD/MD) for paediatrics at 3.0/1.5 mg/kg QD or adults at 200/100 mg QD).

	Neonates (<30 days)	Infants (1 mo to <2 years)	Aged 2 to <5 years	Aged 5 to <18 years	Aged >=18 years)
Number of Subjects	8	23[a]	19	30	83
AUC0-24ss [µg*h /mL]					
Mean (SD)	80.77 (28.03)	82.91 (43.74)	82.81 (31.9)	86.77 (31.12)	91.11 (38.93)
Median (Range)	83.87 (29.27-124.97)	67.52 (49.09-260.64)	80.01 (35.8-161.65)	80.49 (28.3-197.79)	85.09 (30.8-246.9)
90% CI	41.68 - 114.78	50.13 - 111.98	38.55 - 138.86	57.85 - 124.45	43.36 - 154.72
Cminss [µg/mL]					
Mean (SD)	2.64 (0.99)	2.46 (1.44)	2.51 (1.11)	2.52 (0.96)	2.71 (1.31)
Median (Range)	2.59 (0.81-4.09)	1.92 (1.17-8.12)	2.46 (1.01-5.36)	2.34 (0.62-5.9)	2.47 (0.87-9.06)
90% CI	1.28 - 3.88	1.27 - 3.69	1.02 - 4.32	1.59 - 3.76	1.31 - 4.72
CL [L/h/kg]					
Mean (SD)	0.023 (0.0125)	0.0208 (0.0064)	0.0214 (0.0088)	0.0198 (0.0079)	0.0175 (0.0065)
Median (Range)	0.0197 (0.012-0.0525)	0.0212 (0.0058-0.0316)	0.0212 (0.0093-0.0487)	0.0193 (0.0093-0.053)	0.0162 (0.0068-0.0354)
90% CI	0.0136 - 0.0422	0.013 - 0.0304	0.0115 - 0.0354	0.012 - 0.0269	0.009 - 0.0296
Vss [L/kg]					
Mean (SD)	1.1023 (0.4085)	0.7731 (0.2301)	0.9049 (0.275)	0.7528 (0.158)	0.7526 (0.2234)
Median (Range)	1.0166 (0.6036-1.6821)	0.7545 (0.2486-1.3173)	0.8847 (0.5911-1.717)	0.7815 (0.4996-1.1104)	0.7046 (0.3398-1.4875)
90% CI	0.6244 - 1.6598	0.4764 - 1.2678	0.6283 - 1.4853	0.5084 - 0.9509	0.4705 - 1.1418

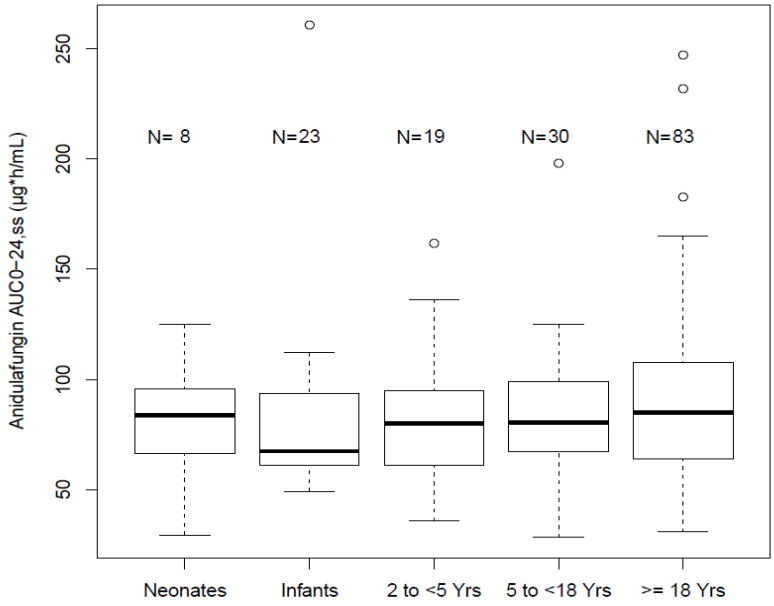
ePharmacology artifact ID RA15257445.
$AUC_{0\text{-}24ss}$:area under the curve over a 24-hour dosing interval at steady state (maintenance dose); CL:clearance; Vss:volume of distribution at steady state
C_{minss}: minimum concentration at steady state (maintenance dose); SD: standard deviation; CI: confidence interval; QD: once daily; mo: month.
[a] Includes 6 subjects from Duke IIR study and 17 subjects from Study A8851008.

Table PK 7. Summary of estimated anidulafungin exposure in paediatric subjects by age groups in study A8851008 (LD/MD doses for paediatric at 3.0/1.5 mg/kg QD).

	Infants (1 mo to <2 years)	Aged 2 to <5 years	Aged 5 to <18 years
Number of Subjects	17	19	30
AUC0-24ss [µg*h/mL]			
Mean (SD)	69.87 (17.65)	82.81 (31.9)	86.77 (31.12)
Median (Range)	66.42 (49.09-112.09)	80.01 (35.8-161.65)	80.49 (28.3-197.79)
90% CI	49.84 - 99.57	38.55 - 138.86	57.85 - 124.45
Cminss [µg/mL]			
Mean (SD)	1.98 (0.58)	2.51 (1.11)	2.52 (0.96)
Median (Range)	1.85 (1.17-3.27)	2.46 (1.01-5.36)	2.34 (0.62-5.9)
90% CI	1.24 - 2.94	1.02 - 4.32	1.59 - 3.76

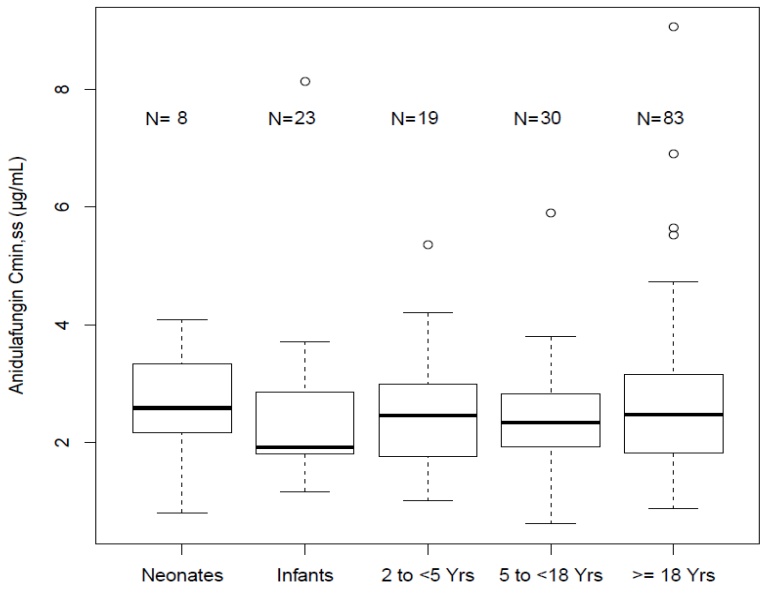
ePharmacology artifact ID RA15793071.
AUC0-24ss: area under the curve over a 24-hour dosing interval at steady state (maintenance dose); LD: loading dose; MD: maintenance dose;
Cminss: minimum concentration at steady state (maintenance dose); SD: standard deviation; CI: confidence interval; QD: once daily; mo: month.

Figure PK 6. Estimated steady-state anidulafungin AUC0-24,ss by age group at studied IV doses (LD/MD doses for paediatric at 3.0/1.5 mg/kg QD or adults at 200/100 mg QD).



ePharmacology artifact ID RA15257446.
AUC0-24ss: area under the curve over a 24-hour dosing interval at steady state (maintenance dose).
IV: intravenous; QD: once daily; LD: loading dose; MD: maintenance dose.
The horizontal line at the center of the box is the median; the box represents the inter-quartile range (from lower (25% percent) to upper (75% percent)); upper and lower whiskers represent data within 1.5 times the inter-quartile range and outliers are represented by dots outside of the whiskers.

Figure PK 7. Estimated steady-state anidulafungin Cmin,ss by age group at studied IV doses (LD/MD doses for paediatric at 3.0/1.5 mg/kg QD or adults at 200/100 mg QD).



ePharmacology artifact ID RA15257447.
Cminss: minimum concentration at steady state (maintenance dose).
IV: intravenous; QD: once daily; LD: loading dose; MD: maintenance dose.
The horizontal line at the center of the box is the median; the box represents the inter-quartile range (from lower (25% percent) to upper (75% percent)); upper and lower whiskers represent data within 1.5 times the inter-quartile range and outliers are represented by dots outside of the whiskers.

The overall evaluation of these exposure data indicates that the currently proposed IV dosing regimen (a 3.0 mg/kg [not to exceed 200 mg] LD followed by 1.5 mg/kg [not to exceed 100 mg] MD QD) is appropriate for use across all paediatric and adolescent age groups (1 month to <18 years old) since the anidulafungin exposures achieved are comparable to those in adults at the recommended dosing regimen (200 mg LD/100 mg MD QD).

Estimated allometric exponents to describe the body weight relationship were used in the PopPK model, hence the body weight relationship could be mostly influenced by the adolescent and adult body weights (median in the dataset is 54 kg).

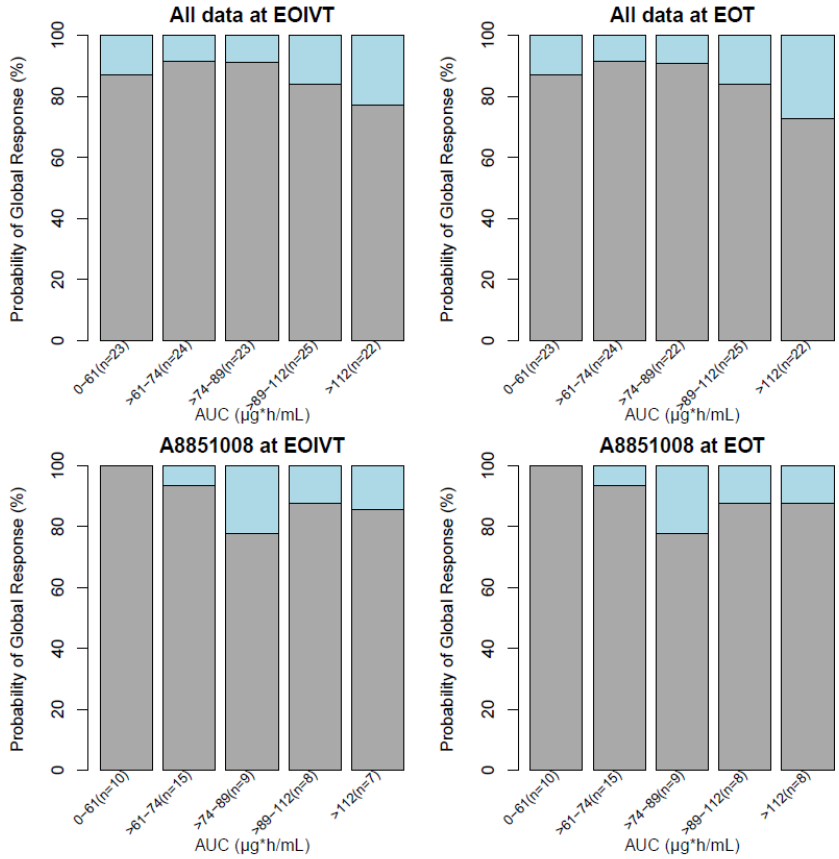
By using theoretical allometric exponents the model performed less well than the model with estimated exponents, with a better fit of the data. Therefore, the model with estimated exponents was considered appropriate for fitting of the data, which is agreed by the CHMP.

Efficacy graphical analysis

Anidulafungin exposure parameters (AUC0-24,ss, Cmin,ss and PK/PD index [AUC0-24,ss/MIC]) were examined graphically as potential predictors for global response at the EOIVT and EOT and all-cause mortality at EOT and EOS including the 6 weeks follow-up in the mITT subjects with PK data. There was a substantial overlap in anidulafungin exposures among the global response success, failure and indeterminate groups. The anidulafungin exposures in subjects who had died overlapped with those in subjects who were alive at EOT and EOS.

Probability of global response of success/failure was evaluated for the mITT subjects (with indeterminate excluded) for AUC0-24,ss quantile groups (quantile <=20%, >20% to 40%, >40% to 60%, >60% to 80%, >80%). The probability of global response (success or failure) for each of the AUC0-24,ss bins for all data and Study A8851008 are presented in Figure 1 (grey area is the probability of success and blue area is the probability of failure). Each bar plot shows the observed probability of the efficacy endpoint, calculated as the ratio of the number of successful outcomes in a particular bin to the total number in that bin and presented as a percentage vs. exposure AUC0-24,ss on the x-axis. Based on these data, global response failure does not appear to be related to lower exposure of anidulafungin in both the overall population and study A8851008.

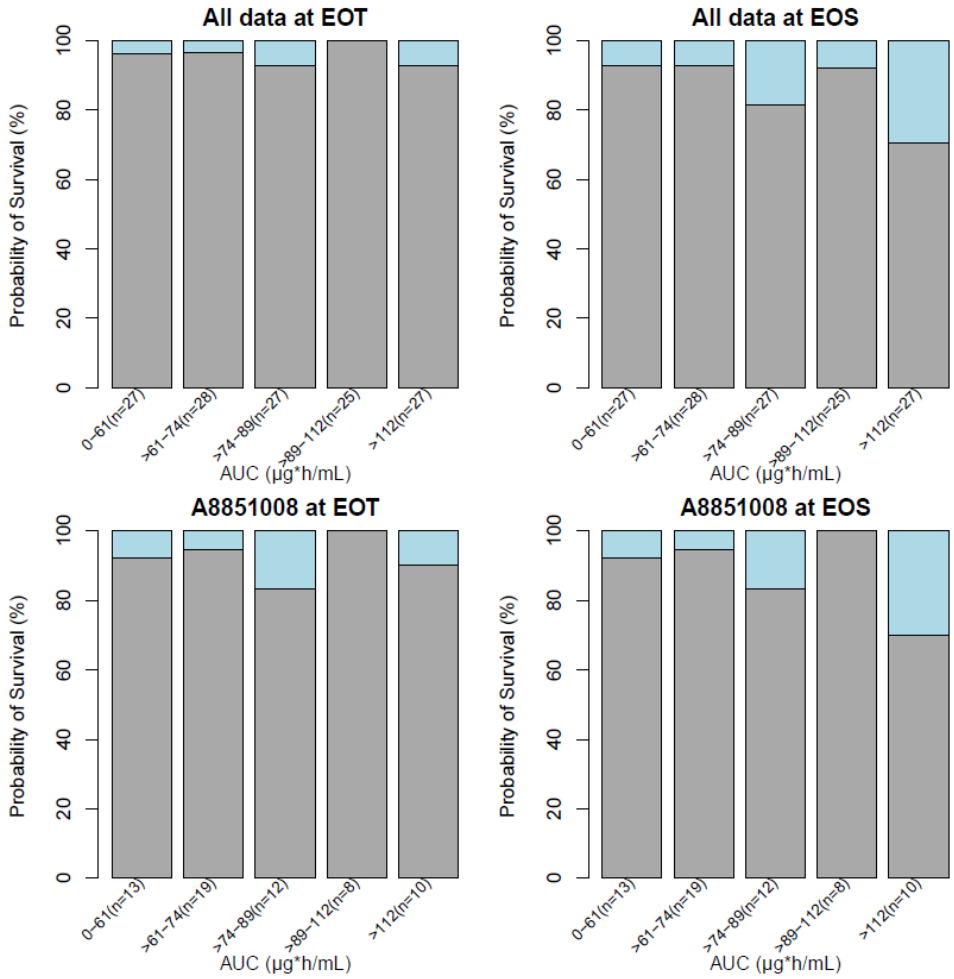
Figure 1. Probability of Global Response vs anidulafungin AUC0-24,ss in mITT subjects with Indeterminate Excluded at EOIVT (Left Panel) and EOT (Right Panel) for all data (upper panel) and study A8851008 (lower panel).



ePharmacology artifact ID RA15263614.
mITT: modified intent-to-treat; EOIVT: end of intravenous therapy; EOT: end of study
n represents number of subjects in the associated AUC0-24,ss bin
The grey areas are the probability of success and the blue areas are the probability of failure

Probability of survival for all data and study A8851008 was similarly evaluated for the 5 AUC0-24,ss quantile groups (figure 2). As there was no clear association observed between anidulafungin exposures and all-cause mortality in both overall population and A8851008, no further exposure-efficacy modeling analysis was performed.

Figure 2. Probability of All-Cause Mortality vs. anidulafungin AUC0-24,ss in mITT subjects at EOT (left panel) and EOS (right panel) for all data (upper panel) and study A8851008 (lower panel).



ePharmacology artifact ID RA15263616.
AUC0-24,ss: area under the curve over a 24-hour dosing interval at steady state.
mITT: modified intent-to-treat; EOT: end of study; EOS: end of study including follow-up period
The grey areas are the probability of alive and the blue areas are the probability of death

Safety graphical and modeling analysis

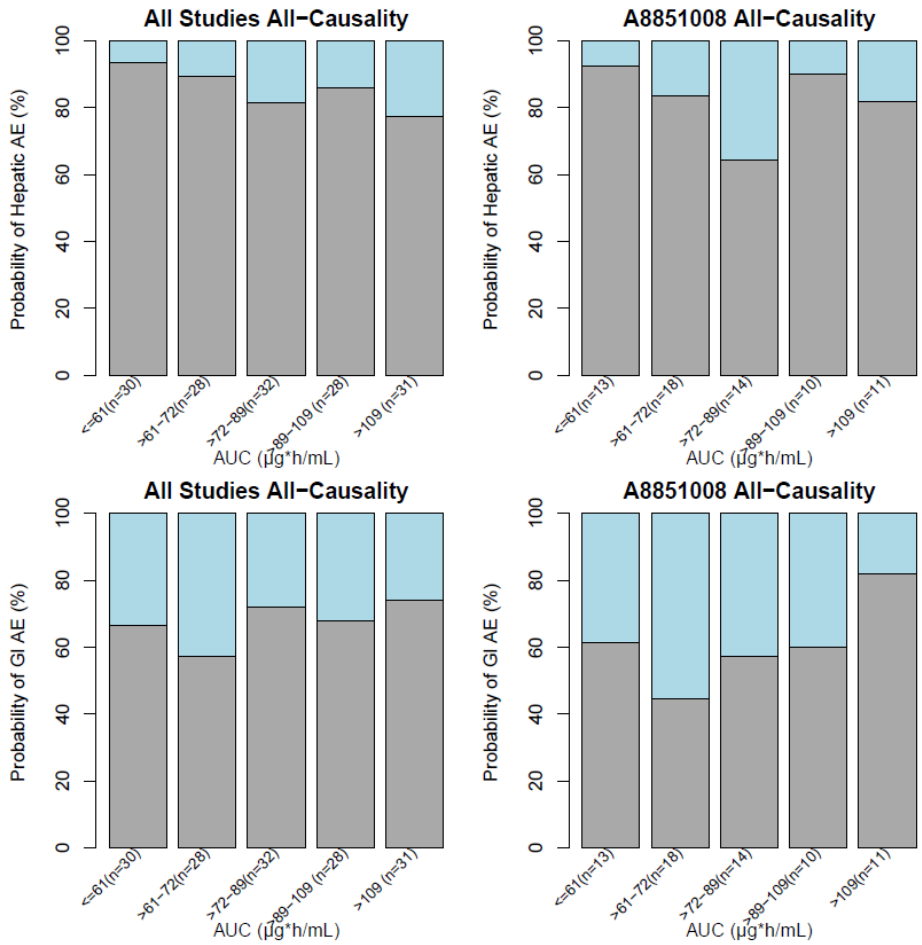
Anidulafungin exposure parameters (AUC0-24,ss and Cmin,ss) were examined graphically as potential predictors for the incidence of hepatic and GI AEs in the safety population with PK data available. There was overlap in anidulafungin exposure metrics among the non-AE and all-causality AEs for non-treatment related as well as for treatment-related AEs.

Similar to the efficacy analysis, the probability of AE was analyzed graphically vs. 5 AUC0-24,ss groups/quantiles. There appears to be a trend towards an increased incidence of all-causality hepatic AEs with higher exposure in the overall population; but there does not appear to be any exposure relationship

for all-causality GI AEs (figure 3) (grey area is the probability without hepatic/GI AEs and blue area is the probability of AEs).

However, when exposure parameters AUC0-24,ss and Cmin,ss were used for further hepatic and GI AEs incidence analyses using a proportional odds model (logistic regression), none of the exposure parameters was identified as a statistically significant predictor for hepatic AE or GI AE incidence. In addition, covariates of interest (age, sex and population) were tested and none of these factors was statistically significant.

Figure 3. Probability of hepatic AE (upper panel) and gastrointestinal AE (lower panel) vs. anidulafungin AUC0-24,ss for all data (left panel) and study A8851008 (right panel) in safety population.



ePharmacology artifact ID RA15839983.
AUC: area under the curve over a 24-hour dosing interval at steady state (maintenance dose);
AE: adverse event; GI: gastrointestinal;
The grey areas are probability of nonAE (not having hepatic or GI AEs). The blue areas are probability of AEs.

Taking the graphical and modeling analyses results together, hepatic or GI AE incidence was not strongly associated with anidulafungin exposures.

The results indicated that there is a trend towards an increased incidence of all-causality hepatic AEs with higher exposure in the overall population. With regards to anidulafungin-related treatment-emergent hepatic AEs, although a some what higher incidence at higher AUCs, no clear exposure-AE trends were observed.

2.3.5. Discussion on clinical pharmacology

A two-compartment PK model with first-order elimination adequately described the anidulafungin data from paediatric and adult subjects with ICC infections or those at risk for invasive fungal infections. Body weight was a structural covariate on CL, Vc, and Vp. PK parameters of anidulafungin were not affected by age and sex. In the model estimated allometric exponents to describe the body weight relationship was used, while it is advised by the EMA MSWP Q&A to investigate theoretical allometric exponents. The MAH was requested to provide such data. They explained that, by using theoretical allometric exponents, the model performed less well than the model with estimated exponents, with a better fit of the data. Therefore, the model with estimated exponents was considered appropriate for fitting of the data. The MAH argument was acceptable and agreed upon.

To be noted, anidulafungin is not metabolised by the liver. Under physiological pH and temperature it is opened to a peptide with an open ring which is further metbolsied by peptide degradation. It is thus not expected that maturing issues in neonates of metabolic pathways play an important role.Based upon the popPK analysis, the proposed IV dosing regimen (3.0 mg/kg LD followed by 1.5 mg/kg MD QD) is considered appropriate for paediatric use since the anidulafungin exposures achieved with this regimen in paediatric subjects are comparable to that in adults at the recommended dosing regimen (200 mg LD/100 mg MD QD). However, in the individual studies the differences in exposure in paediatrics and adults appeared to be much more pronounced. In the Duke IIR study combined exposure data of infants and neonates was comparable to those observed in adults, however in neonates the exposure is about 27% lower and in infants the exposure is about 21% higher compared to adults. Also, in study A8851008 in the 6 sub-study subjects exposure was lower compared to adults. The MAH clarified that although individual studies showed some differences in PK, it should also be noted that a high variability is observed in paediatrics. Moreover, also in some adult studies a high variability and lower exposure has been observed. No clear relationships between anidulafungin exposure parameters and efficacy were identified in paediatric and adult subjects with ICC. The overall popPK data, however, indicated comparable median exposures with a large range in individual values for infants. As there was no clear exposure response identified, this was not considered of concern.

No statistically significant relationships between anidulafungin exposures and incidence of anidulafungin treatment-emergent all-causality hepatic or GI AEs were identified in the combined paediatric and adult dataset. With regards to anidulafungin-related treatment-emergent hepatic AEs, although a somewhat higher incidence at higher AUCs, no clear exposure-AE trends are observed.

2.3.6. Conclusions on clinical pharmacology

The proposed IV dosing regimen (3.0 mg/kg LD followed by /1.5 mg/kg MD QD) is considered appropriate for paediatric use since the anidulafungin exposures achieved with this regimen in paediatric subjects are comparable to that in adults at the recommended dosing regimen (200 mg LD/100 mg MD QD).

2.4. Clinical efficacy

2.4.1. Main study

A8851008 - A Prospective, Open-Label Study to Assess the Pharmacokinetics, Safety and Efficacy of Anidulafungin when used to Treat Children with Invasive Candidiasis, including Candidemia

Methods

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 paediatric patients 1 month to <18 years of age.

Considering the single-arm design of the study, inferences will be limited.

Study participants

The inclusion and exclusion criteria changed during the course of the study (see also under conduct of the study). Below are the inclusion criteria as per the final protocol amendment affecting these, Protocol Amendment 9, dated 16 September 2016.

Prior to protocol Amendment 9 and at the time of enrolment, subjects must have had either a confirmed diagnosis of ICC (based on the growth of Candida spp. from a culture obtained from a normally sterile site within 96 hours prior to enrolment), or mycological evidence highly suggestive of Candida spp. Subjects may have been enrolled and initiated study treatment prior to culture confirmation of Candida spp. If positive culture confirmation for Candida spp. was not obtained subjects were discontinued from treatment; however, such subjects remained in the study for continued safety monitoring for up to 6 weeks after the last dose of study drug.

Subjects had to meet all of the following **inclusion criteria** to be eligible for enrolment into the study:

1. Subject must be either (1) at high risk for candidiasis or (2) have a definitive diagnosis of invasive candidiasis/candidemia (ICC), as defined below:

a. At high risk for candidiasis (subjects 1 month to < 2 years of age only):

Subject is at high risk for candidiasis and antifungal therapy with anidulafungin for a minimum of 5 days is considered appropriate by the investigator.

--OR--

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

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

Microbiologic Criteria:

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

- Candidemia: At least one blood culture positive for Candida sp. (in the absence of other demonstrated foci of infection) or;
- Other forms of invasive candidiasis:
- Positive culture for Candida sp. from a specimen from a normally sterile site (other than blood), with or without a positive blood culture;
- Positive culture for Candida sp. from a percutaneous drain (eg, chest tube, intra-abdominal) placed <24 hours in a normally sterile site;
- Positive blood culture for Candida sp. plus ophthalmic examination consistent with Candida endophthalmitis;
- Candida endocarditis (not applicable to Korean and Portuguese investigator sites): At least one positive blood culture for Candida sp. and evidence of endocarditis on echocardiogram;
- Candida osteomyelitis (not applicable to Korean and Portuguese investigator sites): At least one positive culture for Candida sp. from a bone biopsy or aspirate and evidence of osteomyelitis on a magnetic resonance imaging (MRI) study;

Clinical Criteria:

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

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

  Subjects may be enrolled in the study and initiate study treatment on the basis of mycologic evidence highly suggestive of Candida sp. (e.g., the growth of yeast in culture and/or the direct microscopic visualization of yeast, hyphae, or pseudohyphae) from a sample obtained from a normally sterile site (eg, blood and/or tissue). If culture confirmation of Candida sp. is not obtained, subjects may remain in the study and receive study treatment at the discretion of the investigator. Should the investigator choose to withdraw the subject from study treatment, the subject will discontinued treatment but will remain in the study for continued safety monitoring for up to 6 weeks after the last dose of study treatment. Refer to Section 6.5 and Section 6.6 for follow-up visit requirements.

  Positive cultures for Candida sp. from urine (in the absence of clinical signs and symptoms of pyelonephritis), sputum, bronchoalveolar lavage (BAL), endotracheal aspiration, gastric drainage or gastric aspiration do not qualify as a positive culture for definitive diagnosis of ICC.

2. Male or female between the ages of 1 month and <18 years.
3. Male and female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the treatment period and up to the 6 week follow-up visit. A subject is of

childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

4. For each subject, parent or legal guardian must be willing and able to provide signed and dated written informed consent documentation. Assent from the child or adolescent will be obtained as appropriate. This is to be obtained prior to enrolment.
5. Will be available for the duration of the study and be able to abide by the study restrictions.

Exclusion Criteria

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

1. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.
2. Premature neonates born at gestation of less than 36 weeks (unless the sum of gestational age plus chronological age is at least 44 weeks).
3. Known history of intolerance, allergy, hypersensitivity or serious reaction to anidulafungin or any of its excipients (including fructose), or to other echinocandin antifungals.
4. Pregnant females; breastfeeding females; males and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception during the treatment period and up to the 6 week follow-up visit.
5. Subjects who have failed antifungal therapy with any systemic echinocandin for this episode of candidiasis/candidemia. Recurrence within 2 weeks is considered failure of previous therapy.
6. Subjects with any of the following abnormal laboratory values: Total bilirubin, AST or ALT >5 times the upper limit of normal (ULN).
7. Subjects who require continued treatment with another systemic antifungal agent [oral nonabsorbable azoles (eg, clotrimazole troches) will be permitted]. Exception: the first 6 subjects enrolled who are between 1 month to <2 years of age may receive a second systemic antifungal agent at the investigator's discretion.
8. Subjects with poor venous access that would preclude IV drug delivery or multiple blood draws.
9. Subjects who have participated in a study of an investigational drug or device (without any FDA and EMA approved indications) within four weeks of study entry. The investigational use of licensed agents are permitted if the subject is on a stable regimen for four weeks prior to study start, and expected to remain on the stable regimen for the duration of the trial.
10. Life expectancy <72 hours.
11. Subjects with suspected Candida meningitis. (For Korean and Portuguese investigator sites only: Subjects with suspected Candida endocarditis and Candida osteomyelitis are also excluded.)
12. Subjects with a prosthetic device and/or vascular catheter (including central venous catheter or an implantable port) at a suspected site of infection are to be excluded, unless the device is removed or in situations where catheter salvage is desirable due to the subject's clinical condition.
13. Subjects with a vascular graft suspected to be the site of the Candida infection and positive blood cultures.
14. Subjects with prosthetic or native valve Candida endocarditis who have not and/or cannot undergo valvular replacement surgery prior to or soon after study entry. (not applicable to Korean and Portuguese investigator sites.)
15. Subjects with Candida osteomyelitis associated with a prosthetic device in whom the prosthetic device has not been and/or cannot be removed surgically prior to or soon after study entry. (Not applicable to Korean and Portuguese investigator sites.)
16. Other severe acute or chronic medical or psychiatric condition, electrocardiogram (ECG) abnormalities, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

Inclusion and exclusion criteria changed during the course of the study. The protocol was updated to broaden the study population to include children aged 1 month to <2 years only who were at high risk for candidiasis, in order to accelerate the availability of PK and safety data in this lowest age group as requested by the PDCO. This could have changed the study population over the course of the study. The most impactful change in the protocol consists of protocol amendment 9.

The MAH mentioned that despite the broadened entry criteria applied in Amendment 9, subjects enrolled under Amendment 9 were generally similar to those enrolled prior to the amendment, with only 2 subjects enrolled as being at high risk for ICC without microbiologically confirmed ICC. No further analyses are requested to analyse the impact of these protocol changes.

Treatments

All study subjects received anidulafungin IV treatment (3.0 mg/kg loading dose on Study Day 1 followed by 1.5 mg/kg maintenance dose daily thereafter). Subjects were to receive anidulafungin IV for a minimum of 10 days to a maximum of 35 days. There was an option to switch to oral treatment with fluconazole (6 to 12 mg/kg/day, maximum 800 mg/day) after at least 10 days of IV treatment, provided the subject met pre specified criteria.

Subjects who were enrolled under Amendment 9 without microbiologically confirmed Candida infection were treated with IV anidulafungin (3.0 mg/kg loading dose on Study Day 1 followed by 1.5 mg/kg maintenance dose daily thereafter) at the discretion of the Investigator for a minimum of 5 days to a maximum of 35 days.

Objectives

The primary objective of the study was:

- To assess the safety and tolerability of anidulafungin, when used to treat children with ICC.

The secondary objectives of the study were:

- To assess the efficacy of anidulafungin, as measured by global response, at the following time points: end of IV treatment (EOIVT), end of treatment (EOT), and 2- and 6-week follow-up visits.
- To explore PK parameters of anidulafungin in children aged 1 month to <2 years following IV infusion of anidulafungin: area under the curve over the 24-hour dosing interval (AUC24) and maximum plasma concentration (Cmax).
- To explore PK parameters of polysorbate 80 following IV infusion of anidulafungin AUC24 and Cmax.
- To explore the exposure-response (safety and efficacy endpoints) relationship of anidulafungin using a nonlinear mixed effects approach as appropriate, including exploring the association between the PK/pharmacodynamic (PD) index, eg, AUC/minimum inhibitory concentration (MIC) and efficacy endpoints.
- To assess rates of relapse (recurrence) at the 2- and 6-week follow-up visits.
- To assess rates of new infection at the 2- and 6-week follow-up visits.
- To assess all-cause mortality during study treatment and follow-up visits.

Outcomes/endpoints

Primary Endpoint

- Safety and tolerability of anidulafungin.

Secondary Endpoints

- Global response of success, failure, or indeterminate at the EOIVT and subsequent time points (see description below)
- Pharmacokinetic parameters of anidulafungin in children aged 1 month to <2 years following IV infusion of anidulafungin: AUC24 and Cmax;
- Exposure-response (efficacy and safety endpoints) relationships of anidulafungin using a nonlinear mixed effects approach as appropriate;
- Rates of relapse at the Week 2 and Week 6 FU visits;
- Rates of emerging infection at the Week 2 and Week 6 FU visits;
- All-cause mortality during study therapy and follow-up visits.

Global response was defined as:

- Success: A subject was categorized as a success if there was both a clinical response of success (cure or improvement) and microbiological response of success (eradication or presumed eradication).
- Failure: A subject was categorized as a failure if there was a clinical response of failure and/or a microbiological failure (persistence or new infection at follow-up or relapse of infection at follow-up).
- Indeterminate: A subject was categorized as indeterminate if there was a clinical response of indeterminate and/or microbiological response of indeterminate and neither response was a failure.

Table 3. Summary of Clinical and Microbiological Response Assessment - Subjects with Invasive Candidiasis, including Candidemia (Except for Subjects with *Candida* endocarditis or *Candida* osteomyelitis)

Clinical Response at EOIVT, EOT, and the 2- and 6-Week Follow-Up Visits[a]	Microbiological Response at EOIVT and EOT	Microbiological Response at the 2- and 6-Week Follow-Up Visits[a]
Cure: Resolution of signs and symptoms attributed to *Candida* infection; no additional systemic antifungal. **Improvement**: Significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal. **Failure**: No significant improvement in signs and symptoms, or death due to the *Candida* infection. Subjects must have received at least 3 doses of study medication to be classified as a failure. **Indeterminate**: Evaluation was not made due to withdrawal from the study prior to assessment of cure or failure. Subjects who received fewer than 3 doses of study medication were assigned a clinical response of indeterminate.	**Eradication or presumed eradication**: Baseline pathogen not isolated from original site culture(s), or culture data not available for a subject with successful outcome. **Persistence (documented or presumed)**: Any baseline *Candida* spp. was present in repeat cultures, or culture data were not available for subject with a clinical outcome of failure. **Indeterminate**: Culture data were not available for a subject with a clinical outcome of indeterminate.	**Eradication or presumed eradication**: Baseline pathogen not isolated from original site culture(s), or culture data not available for a subject with successful outcome. **Persistence (documented or presumed)**: Any baseline *Candida* spp. was present in repeat cultures, or culture data not available for subject with a clinical outcome of failure. **Indeterminate**: Culture data were not available for a subject with a clinical outcome of indeterminate. **Relapse (recurrence)**: Any baseline *Candida* spp. isolated following eradication (documented or presumed); or culture data were not available for a subject with a clinical response of failure after a previous response of success. **New Infection**: Subject presenting with clinical failure with the emergence of new *Candida* spp. at the original site of infection or at a distant site of infection.

In cases where the subject received concomitant antifungal use with activity for any baseline Candida spp., the following algorithms were used for determining global response at EOIVT, EOT, and 2- and 6-week follow-up visits.

- If a subject took 2 or more days of antifungal medications (as identified by the clinical team) after the start of study medication until EOT for any reason, the subject was imputed to failure for all visits that occurred after the antifungal medication was taken.
- If a subject took 1 day of antifungal medication after the start of study treatment until EOT for the reason "lack of efficacy" the subject was similarly imputed to failure for all visits that occurred after the antifungal medication was taken. The clinical team determined whether the antifungal medication was used for "lack of efficacy".
- In the follow-up period, if a subject took at least 1 day of antifungal medication for reason of "lack of efficacy", the subject was imputed to failure for all visits that occurred after the antifungal medication was taken. Again, the clinical team determined whether the antifungal medication had been used for "lack of efficacy".

Primary and secondary outcomes were considered appropriate by the CHMP.

Sample size

Since this was a descriptive study, sample size calculations were not performed. A sample size of 60 evaluable subjects for this study was chosen for assessing safety and tolerability, PK, and efficacy in children with ICC. Subjects evaluable for efficacy were those that had received at least 1 dose of study drug and had a confirmed Candida infection.

Randomisation

The study was single armed.

Blinding (masking)

The study was open-label.

Statistical methods

Analyses populations

The set of subjects for primary (safety) evaluation was **the Safety population,** defined as all subjects with at least 1 dose of study medication.

Secondary efficacy analyses were to be assessed in the **Modified Intent-to-Treat (MITT) population**, defined as all subjects who have received at least one dose of study drug and who have microbiological evidence of Candida infection.

PP population: subjects in the MITT population, who also:

- Completed a minimum of 10 days of IV anidulafungin treatment, unless declared a clinical and/or microbiological failure.
- Received total antifungal treatment (IV only or IV plus oral) for a minimum duration of 14 days, unless declared a clinical and/or microbiological failure.
- Had not received more than 48 hours of systemic antifungal therapy (for treatment of current Candida infection) prior to first dose of study drug.
- Must not have had 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 the first dose of study drug (prior to protocol Amendment 9).
- Had not taken more than 1 day of protocol prohibited antifungal therapy concomitant with study drug, unless declared a clinical and or microbiological failure.
- Reached the 6-weeks follow-up visit unless the subject died or withdrew consent prior to 6-week follow-up.
- Had no protocol violations that could have an impact on the efficacy endpoints.

PK population: subjects who received a known amount of anidulafungin and who had 1 or more PK sample collected

Analyses

The primary analysis was the evaluation of adverse events throughout the trial, laboratory tests, temperature, and physical examination. The following parameters were to be summarized: rates of discontinuation, adverse events, and laboratory abnormalities. Safety data was to be descriptively summarized. Descriptive statistics for categorical data was to include frequencies and/or percentages.

The efficacy analysis would an assessment of global response:

- Global Response

Efficacy was based on a determination of global response (combination of clinical and microbiological response as assessed by the Investigator) of success, failure, or indeterminate. For each age category, analysis of the global response at the EOIVT, EOT, and 2- and 6-week follow-up visits was performed for the Modified Intent-to-Treat (MITT) and Per-Protocol (PP) populations. The summary included the number of observations and estimated response rates overall and in each age category.

This analysis was also performed by site of infection and by baseline *Candida spp*., combined across the age groups.

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

In addition to global response, summaries of clinical response, and microbiological response were also produced for the MITT and PP populations, and were presented overall, by each age category, by site of infection, and by each *Candida spp*.

For clinical response, the number of subjects in each of the categories 'Cure', 'Improvement', 'Failure', 'Indeterminate', and 'Missing' were presented. For microbiological response, the number of subjects in each of the categories 'Eradication', 'Presumed Eradication', 'Persistence', 'Recurrence of Infection', 'New Infection', 'Indeterminate', and 'Missing' were presented.

- Relapse (Recurrence)

For each age category, the number and percentage of subjects with relapse at the 2- and 6-week follow-up visits were calculated for the MITT population. The denominator for relapse was the number of subjects in the population at baseline.

- New Infection

For each age category, the number and percentage of subjects who had new infection at the 2- and 6-week follow-up visits were calculated for the MITT population. The denominator for the new infection was the number of subjects in that group and population at baseline.

- All-Cause Mortality

For each age category, analysis of all-cause mortality during study treatment and follow-up visits was performed in the safety and MITT populations. Mortality at each time point was presented with exact 95% CIs for binomial proportion, using the Clopper-Pearson method which employs the F-distribution to obtain percentiles of the binomial distribution. All causes of death were summarized.

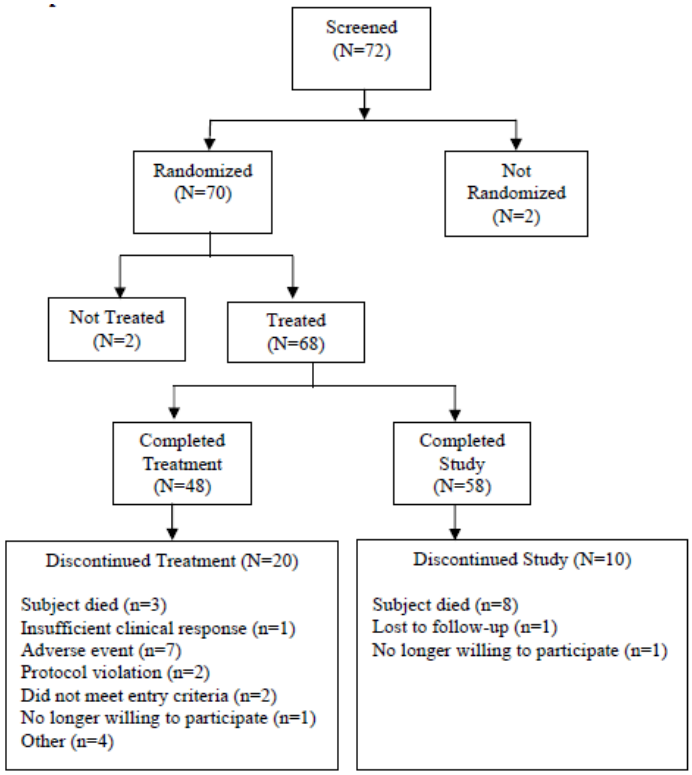
- Time to Death

Time to death (all-cause) was analyzed using the safety and MITT populations. For each age category, the number of subjects who died during the study reporting period was summarized by age stratum.

Results

Participant flow

Figure 5.4. 1 Subject disposition (A8851008)



Source: Tables 14.1.1.1, 14.1.1.2, and 14.1.1.3.
Abbreviations: N=number of subjects in population or population; n=number of subjects with an event.

Recruitment

Study Initiation Date: First Subject First Visit (FSFV): 27 Feb 2009

Primary Completion Date: Last Subject Last Visit (LSLV): 14 Feb 2018

Over the 9-year study duration, subjects were enrolled at 26 sites in 10 countries (Brazil, Canada, Greece, Italy, Republic of Korea, Russia, Spain, Taiwan, United Kingdom [UK], and United States [US]), and an additional 47 sites were supplied study drug but did not enrol any subjects. Study sites were established in 3 countries (France, Germany, and Portugal) that did not screen any subjects.

The CHMP noted that recruitment into the trial was challenging and the duration of the study may have resulted in patients who were recruited earlier in the study no longer being comparable to patients recruited later in the study.

Conduct of the study

During the course of the study, 9 protocol amendments were implemented. Most significant amendments are listed here. Amendment 4 (2010) modified the entry criteria to allow enrolment of patients with Candida endocarditis or osteomyelitis. Amendment 8 (2015) added measurement of plasma concentrations of polysorbate 80 in the youngest age. Due to ongoing challenges in enrolling sufficient numbers of patients in the youngest age cohort (1 month to <2 years), Amendment 9 (2016) broadened the study population to align with regulatory agency feedback and to ensure that adequate numbers of appropriate patients were enrolled; in this latter amendment, patients at risk for Candida infection were permitted to be enrolled, in addition to the original target population, which was required to have confirmed Candida infection.

Protocol deviations

Table 6. Potentially Important Protocol Deviations by Age Group and Overall

Category Sub-category	Age Group 1 Month to <2 Years (N=20)		2 to <5 Years (N=20)		5 to <18 Years (N=32)		Overall (N=72)	
	PDs	n (%)	PDs	n (%)	PDs	n (%)	PDs	n (%)
Concomitant medications	0	-	1	1 (5.0)	3	3 (9.4)	4	4 (5.6)
Received >1 day other systemic antifungal therapy during FU	0	-	1	1 (5.0)	2	2 (6.3)	3	3 (4.2)
Received >1 day other systemic antifungal therapy during treatment	0	-	0	-	1	1 (3.1)	1	1 (1.4)
Inclusion/exclusion criteria	5	4 (20.0)	4	4 (20.0)	4	4 (12.5)	13	12 (16.7)
No qualifying study condition	1	1 (50.0)	1	1 (5.0)	0	-	2	2 (2.8)
Infected device/catheter not removed within 48 hr of study entry	3	2 (10.0)	0	-	1	1 (3.1)	4	3 (4.2)
Qualifying culture >96 hr from study entry	0	-	1	1 (5.0)	0	-	1	1 (1.4)
Received >48 hr systemic antifungal therapy	1	1 (5.0)	2	2 (10.0)	1	1 (3.1)	4	4 (5.6)
Total bilirubin, ALT, AST >5 × ULN	0	-	0	-	2	2 (6.3)	2	2 (2.8)
Informed consent	1	1 (5.0)	3	2 (10.0)	6	5 (15.6)	10	8 (11.1)
Both parents did not sign per local requirement	0	-	2	2 (10.0)	5	5 (15.6)	7	7 (9.7)
HIPAA/data privacy form not signed	0	-	0	-	1	1 (3.1)	1	1 (1.4)
Revised/updated ICD not signed at FSFV	0	-	1	1 (5.0)	0	-	1	1 (1.4)
Subject/guardian signed ICD after screen/enroll date	1	1 (5.0)	0	-	0	-	1	1 (1.4)

Category Sub-category	Age Group						Overall (N=72)	
	1 Month to <2 Years (N=20)		2 to <5 Years (N=20)		5 to <18 Years (N=32)			
Investigational product	55	15 (75.0)	94	15 (75.0)	124	29 (90.6)	273	59 (81.9)
Did not meet criteria for oral fluconazole switch	0	-	0	-	1	1 (3.1)	1	1 (1.4)
Improper IP prep/dispense procedures	26	2 (10.0)	4	3 (15.0)	6	5 (15.6)	36	10 (13.9)
Incorrect dosing schedule	3	1 (5.0)	1	1 (5.0)	7	5 (15.6)	11	7 (9.7)
Infusion rate not within specified range	11	3 (15.0)	64	9 (45.0)	71	8 (25.0)	146	20 (27.8)
IP lost	0	-	2	2 (10.0)	0	-	2	2 (2.8)
Lack of source documentation availability	0	-	2	2 (10.0)	1	1 (3.1)	3	3 (4.2)
Missed dose	2	1 (5.0)	0	-	0	-	2	1 (1.4)
Overfill volume not removed from IV bag for all IP doses administered	6	6 (30.0)	9	9 (45.0)	16	16 (50.0)	31	31 (43.1)
Received incorrect dose	3	2 (10.0)	0	-	8	2 (6.3)	11	4 (5.6)
Received <14 days total therapy after second negative culture	4	4 (20.0)	4	4 (20.0)	9	9 (28.1)	17	17 (23.6)
Storage error	0	-	8	2 (10.0)	0	-	8	2 (2.8)
Unexpected amount of oral study drug returned	0	-	0	-	5	1 (3.1)	5	1 (1.4)
Laboratory	49	11 (55.0)	24	12 (60.0)	60	21 (65.6)	133	44 (61.1)
Cultures not obtained as specified in protocol	13	5 (25.0)	3	2 (10.0)	19	11 (34.4)	35	18 (25.0)
Lab not done	33	9 (45.0)	17	10 (50.0)	36	16 (50.0)	86	35 (48.6)
PK sample not done	2	1 (5.0)	0	-	0	-	2	1 (1.4)
PK sample not properly collected/stored/handled	0	-	1	1 (5.0)	2	2 (6.3)	3	3 (4.2)
Sample not sent to central lab	1	1 (5.0)	3	3 (15.0)	2	2 (6.3)	6	6 (8.3)
Source documentation missing	0	-	0	-	1	1 (3.1)	1	1 (1.4)
Procedures/tests	13	7 (35.0)	20	8 (40.0)	19	11 (34.4)	52	26 (36.1)

Category Sub-category	Age Group 1 Month to <2 Years (N=20)		2 to <5 Years (N=20)		5 to <18 Years (N=32)		Overall (N=72)	
	PDs	n (%)	PDs	n (%)	PDs	n (%)	PDs	n (%)
Abnormal procedure/test result not repeated per protocol	0	-	0	-	3	3 (9.4)	3	3 (4.2)
Did not complete clinical and/or microbiological response assessments	1	1 (5.0)	3	2 (10.0)	0	-	4	3 (4.2)
Procedure not performed by medically qualified individual	1	1 (5.0)	1	1 (5.0)	2	1 (3.1)	4	3 (4.2)
Procedure/test not done	11	5 (25.0)	16	5 (25.0)	14	11 (34.4)	41	21 (29.2)
Protocol specific discontinuation criteria	1	1 (5.0)	0	-	1	1 (3.1)	2	2 (2.8)
Noncompliance with d/c criteria for abnormal LFTs	1	1 (5.0)	0	-	1	1 (3.1)	2	2 (2.8)
Randomization	1	1 (5.0)	2	2 (10.0)	4	3 (9.4)	7	6 (8.3)
IP container number assigned but not dispensed correctly	1	1 (5.0)	0	-	0	-	1	1 (1.4)
Randomization procedures not followed properly	0	-	1	1 (5.0)	3	2 (6.3)	4	3 (4.2)
Randomized under wrong stratification	0	-	1	1 (5.0)	1	1 (3.1)	2	2 (2.8)
Safety reporting	4	2 (10.0)	3	2 (10.0)	1	1 (3.1)	8	5 (6.9)
SAE reporting delayed	4	2 (10.0)	3	2 (10.0)	1	1 (3.1)	8	5 (6.9)
Visit schedule	10	7 (35.0)	11	3 (15.0)	18	7 (21.9)	39	17 (23.6)
EOIVT/EOT visit not done	0	ND	0	ND	1	1 (3.1)	1	1 (1.4)
On treatment visit not done	2	1 (5.0)	9	1 (5.0)	7	1 (3.1)	18	3 (4.2)
Visit done outside protocol window	4	4 (20.0)	0	ND	4	4 (12.5)	8	8 (11.1)
Visit incomplete	4	3 (15.0)	2	2 (10.0)	4	3 (9.4)	10	8 (11.1)
Week 2 FU	0	ND	0	ND	1	1 (3.1)	1	1 (1.4)
Week 6 FU	0	ND	0	ND	1	1 (3.1)	1	1 (1.4)

Source: Table 14.1.2.5.
Note: percentages were based on N.
Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; EOT=end of treatment; EOIVT=end of IV treatment; FSFV=First Subject First Visit; FU=follow-up; HIPAA=Health Insurance Portability and Accountability Act; hr=hour; ICD=informed consent document; IP=investigational product; IV=intravenous; LFT=liver function test; N/n=number of subjects; ND=not done; PDs=number of protocol deviations; PK=pharmacokinetic; SAE=serious adverse event; ULN=upper limit of normal.

The CHMP noted that most of the protocol deviations were related to the administration of the investigational product and concerned 'lab not done'.

Baseline data

Demographic characteristics are summarized by age group in Table 9.

Table 9. Demographic Characteristics – Safety Population

	1 Month to <2 Years			2 to <5 Years			5 to <18 Years			Overall		
	Male (N=10)	Female (N=9)	Total (N=19)	Male (N=11)	Female (N=8)	Total (N=19)	Male (N=17)	Female (N=13)	Total (N=30)	Male (N=38)	Female (N=30)	Total (N=68)
Age, years, n (%)	10 (100.0)	9 (100.0)	19 (100.0)	11 (100.0)	8 (100.0)	19 (100.0)	17 (100.0)	13 (100.0)	30 (100.0)	38 (100.0)	30 (100.0)	68 (100.0)
Mean	0.96	0.89	0.93	2.93	3.31	3.09	10.29	11.15	10.67	5.71	5.98	5.83
SD	0.57	0.48	0.52	0.61	0.75	0.68	4.03	3.26	3.68	5.02	5.16	5.05
Range	0.1-1.8	0.3-1.8	0.1-1.8	2.3-4.0	2.3-4.0	2.3-4.0	5.0-17.0	6.0-17.0	5.0-17.0	0.1-17.0	0.3-17.0	0.1-17.0
Race, n (%)												
White	10 (100)	9 (100)	19 (100)	8 (72.7)	7 (87.5)	15 (78.9)	11 (64.7)	9 (69.2)	20 (66.7)	29 (76.3)	25 (83.3)	54 (79.4)
Black	0	0	0	1 (9.1)	0	1 (5.3)	0	0	0	1 (2.6)	0	1 (1.5)
Asian	0	0	0	1 (9.1)	1 (12.5)	2 (10.5)	3 (17.6)	1 (7.7)	4 (13.3)	4 (10.5)	2 (6.7)	6 (8.8)
Other	0	0	0	1 (9.1)	0	1 (5.3)	3 (17.6)	3 (23.1)	6 (20.0)	4 (10.5)	3 (10.0)	7 (10.3)
Weight (kg), n (%)	10 (100.0)	9 (100.0)	19 (100.0)	11 (100.0)	8 (100.0)	19 (100.0)	17 (100.0)	13 (100.0)	30 (100.0)	38 (100.0)	30 (100.0)	68 (100.0)
Mean	8.03	7.71	7.88	14.81	14.36	14.62	36.05	37.98	36.89	22.53	22.60	22.56
SD	3.20	2.86	2.96	3.09	2.89	2.94	20.51	21.58	20.64	18.59	19.76	18.97
Range	2.3-13.0	2.4-11.2	2.3-13.0	10.1-19.0	10.0-19.3	10.0-19.3	13.4-85.0	16.0-85.7	13.4-85.7	2.3-85.0	2.4-85.7	2.3-85.7
Height (cm), n (%)	9 (90.0)	8 (88.9)	17 (89.5)	11 (100.0)	8 (100.0)	19 (100.0)	17 (100.0)	13 (100.0)	30 (100.0)	37 (97.4)	29 (96.7)	66 (97.1)
Mean	69.17	66.09	67.72	95.10	100.94	97.56	138.68	137.92	138.35	108.81	107.90	108.41
SD	18.27	11.32	15.02	10.38	18.09	13.99	20.83	19.72	20.01	34.18	34.82	34.20
Range	41.0-98.0	48.2-79.0	41.0-98.0	70.0-108.0	78.0-139.0	70.0-139.0	108.5-180.0	106.0-163.0	106.0-180.0	41.0-180.0	48.2-163.0	41.0-180.0
BMI (kg/m^2), n (%)				11 (100.0)	8 (100.0)	19 (100.0)	17 (100.0)	13 (100.0)	30 (100.0)	28 (73.7)	21 (70.0)	49 (72.1)
Mean	NA	NA	NA	16.35	14.69	15.65	17.74	18.54	18.08	17.19	17.08	17.14
SD	NA	NA	NA	2.12	3.37	2.76	6.88	6.38	6.56	5.49	5.66	5.51
Range	NA	NA	NA	13.7-20.6	6.8-17.5	6.8-20.6	11.4-38.9	11.0-33.5	11.0-38.9	11.4-38.9	6.8-33.5	6.8-38.9

Source: Table 14.1.2.1.
BMI was calculated as wt/(ht*.01)**2.
BMI was presented in subjects aged > 2 years only as the BMI chart is not recommended for clinical use in children before 2 years of age.
Range=minimum to maximum.
Abbreviations: BMI=body mass index; N=number of subjects in the population; n=number of subjects with characteristic; NA=not available; SD=standard deviation.

A large proportion of subjects had a present medical history indicative of significant underlying disease, including blood and lymphatic system disorders (n=42, 65.6%), infections and infestations (n=40, 62.5%), gastrointestinal disorders (n=38, 59.4%), general disorders and administration site conditions (n=36, 56.3%), metabolism and nutritional disorders (n=34, 53.1%), and neoplasms benign, malignant, and unspecified (including cysts and polyps) (n=24, 37.5%).

The most frequently reported risk factors for Candida infection were the use of broad-spectrum antibiotics and the use of a central venous catheter (50 [78.1%] subjects each) followed by total parenteral nutrition (29 [45.3%] subjects). Nearly a third of subjects overall were receiving chemotherapy, were neutropenic (n=21 each, 32.8%), or were receiving systemic steroids /immunosuppressives (n=20, 31.3%). Approximately 25% of subjects had either surgery or abdominal surgery as a risk factor. Additionally, 16 (25.0%) subjects had an intensive care unit length of stay of at least 4 days, and 11 (17.2%) subjects were mechanically ventilated.

Table 10. Risk Factors for *Candida* Infection - Modified Intent-to-Treat Population

Candidemia Risk Factors	Age Group			
	1 Month to <2 Years (N=16)	2 to <5 Years (N=18)	5 to <18 Years (N=30)	Total (N=64)
Number of subjects (%) with any risk factor	16 (100)	17 (94.4)	28 (93.3)	61 (95.3)
Use of broad-spectrum antibiotics	16 (100)	13 (72.2)	21 (70.0)	50 (78.1)
Use of central venous catheter	12 (75.0)	16 (88.9)	22 (73.3)	50 (78.1)
Total parenteral nutrition	9 (56.3)	8 (44.4)	12 (40.0)	29 (45.3)
Chemotherapy	3 (18.8)	8 (44.4)	10 (33.3)	21 (32.8)
Neutropenia	4 (25.0)	7 (38.9)	10 (33.3)	21 (32.8)
Use of systemic steroids or other immunosuppressives	6 (37.5)	2 (11.1)	12 (40.0)	20 (31.3)
Surgery	8 (50.0)	1 (5.6)	9 (30.0)	18 (28.1)
Abdominal surgery	7 (43.8)	4 (22.2)	5 (16.7)	16 (25.0)
Length of intensive care unit stay of ≥4 days	7 (43.8)	2 (11.1)	7 (23.3)	16 (25.0)
Mechanical ventilation	6 (37.5)	1 (5.6)	4 (13.3)	11 (17.2)
Other	3 (18.8)	1 (5.6)	4 (13.3)	8 (12.5)
Renal insufficiency	0	2 (11.1)	1 (3.3)	3 (4.7)
Dialysis	0	2 (11.1)	0	2 (3.1)
Solid organ transplant	1 (6.3)	0	0	1 (1.6)

Source: Table 14.2.2.
Subjects could have had more than 1 ICC risk factor reported.
Abbreviations: ICC=invasive candidiasis, including candidemia; MITT=Modified Intent-to-Treat; N=number of subjects in the population.

Overall, the most commonly reported baseline pathogens identified in the 64 subjects in the MITT population included *Candida albicans* (25 [39.1%] subjects), *Candida parapsilosis* (17 [26.6%] subjects), and *Candida tropicalis* (9 [14.1%] subjects). Among subjects in the 1 month to <2 years and the 2 to <5 years age groups, *Candida albicans* was the most common baseline pathogen, while *Candida parapsilosis* was the most common baseline pathogen identified in the 5 to <18 years age group. The percent of subjects with *Candida parapsilosis* was lower in the 2 to <5 years age group (11.1%) compared to the other age groups: 31.3% and 33.3% in the 1 month to <2 years and the 5 to <18 years age groups, respectively.

Table 12. Summary of Baseline *Candida* Mycology Results - Modified Intent-to-Treat Population

Genus/species[a]	Age Group			
	1 Month to <2 Years (N=16) n (%)	2 to <5 Years (N=18) n (%)	5 to <18 Years (N=30) n (%)	Overall (N=64) n (%)
Candida albicans	7 (43.8)	10 (55.6)	8 (26.7)	25 (39.1)
Candida parapsilosis	5 (31.3)	2 (11.1)	10 (33.3)	17 (26.6)
Candida tropicalis	2 (12.5)	1 (5.6)	6 (20.0)	9 (14.1)
Candida lusitaniae	0	1 (5.6)	4 (13.3)	5 (7.8)
Candida glabrata	1 (6.3)	2 (11.1)	1 (3.3)	4 (6.3)
Candida guilliermondii	0	2 (11.1)	1 (3.3)	3 (4.7)
Candida famata	0	1 (5.6)	0	1 (1.6)
Candida haemulonii[b]	0	1 (5.6)	0	1 (1.6)
Candida species unspecified[b]	1 (6.3)	0	0	1 (1.6)

Source: Table 14.2.3.
Abbreviations: MITT=Modified Intent-to-Treat; N=number of subjects in the population; n=the number of isolates; spp.=species.
a. As identified by local microbiology laboratory. Subjects could have had multiple *Candida* species at baseline.
b. The reference microbiology laboratory identified the *Candida haemulonii* isolate as *Kodamaea ohmeri* and the unspecified *Candida* spp. isolate as *Candida parapsilosis*.

Prior and concomitant treatments

The 3 most commonly reported prior non-antifungal medications included paracetamol (n=29, 42.6%), meropenem (n=19, 27.9%), and vancomycin (n=18, 26.5%).

The use of prior antifungals for the current episode of Candida infection was permitted up to a maximum of 48 hours for subjects enrolled prior to protocol Amendment 9, unless the antifungal was administered as prophylaxis. Three subjects received systemic antifungal therapy >48 hours prior to the first dose of study drug and were excluded from the PP population on this basis.

A total of 46 (67.6%) subjects received systemic antifungals prior to the start of study drug. The most commonly used prior antifungal agents were fluconazole (29.4%), amphotericin B (13.2%), caspofungin, itraconazole, and micafungin (all 5.9%), and amphotericin B, liposome (4.4%). No notable trends were identified by age group.

The 3 most commonly reported concomitant medications overall were paracetamol (n=29, 42.6%), vancomycin (n=25, 36.8%), and furosemide (n=23, 33.8%).

Among the 64 patients enrolled in the MITT population, concomitant antifungal use was reported as follows:

- 18 patients (28.1%) received no other systemic antifungal agents apart from anidulafungin during the study,
- 31 patients (48.4%) were switched to oral fluconazole following anidulafungin, as permitted by the protocol; among these, 4 patients received additional fluconazole and/or other systemic antifungals during the post-treatment follow-up (FU) period and 1 patient died during the period of treatment with oral fluconazole,
- 15 patients (23.4%) were not switched to oral fluconazole and received systemic antifungal treatment other than anidulafungin during the study. The majority of these cases were due to treatment failure and/or discontinuation from study treatment due to an AE. As per the protocol, patients switched to other antifungal agents following discontinuation from study treatment (for any reason) were to be followed through the 6-week follow-up visit.

The most commonly used treatment was fluconazole, which was used as prophylaxis (per protocol), for 11 [16.2%] subjects).

Those subjects who received antifungal drug treatment that was not used as prophylaxis between EOT and prior to the 6-week follow-up visit were considered clinical failures based on the algorithm.

The CHMP considered that baseline criteria are reflective of a patient population at high risk of ICC, with substantial underlying morbidity, high rates of underlying malignancies, high rate of parenteral nutrition, and substantial use of concomitant medication. Thirty-three % of subjects was neutropenic; similar proportions of patients were receiving chemotherapy or were receiving systemic steroids /immunosuppressives. The most prevalent baseline pathogens were Candida parapsilosis and Candida albicans.

The Committed noted that the Dossier section on concomitant treatments states that overall 19 (27.9%) subjects received antifungal drug treatment between EOT and prior to the 6-week follow-up visit. Upon request, the MAH clarified that, apart from 31 patients who switched to oral fluconazole as permitted by the protocol, most instances in which other systemic antifungal therapies were used were due to treatment failures (n=7) and / or discontinuations from treatment (n=4). In addition, 18 subjects did not receive any systemic antifungal agent and 4 subjects received systemic antifungal agents other than oral fluconazole after completion of IV treatment with anidulafungin.

Numbers analysed

Of the 72 screened subjects, 4 subjects did not receive study drug and were not included in the safety population: 2 subjects [redacted] were screen failures and 2 subjects [redacted] were not included due to protocol violation (permitted window for prior antifungal therapy had elapsed). Of the 68 subjects in the safety population, 64 were included in the MITT population, ie, these subjects had received at least 1 dose of study drug and had microbiological confirmation of Candida infection. Two subjects [redacted] were excluded from the MITT population when final results of their screening cultures did not show growth of *Candida spp.,* rather one culture was positive for *Exophiala (Wangiella*) dermatitidis and the other positive for *Malssezia furfur*. Two additional subjects [redacted] were excluded from the MITT population as they were enrolled under Amendment 9 as being at high risk of IC and did not have microbiologically-confirmed ICC.

Table 7. Summary of Analysis Populations

	Age Group			Overall (N=72) n (%)
	1 Month to <2 Years (N=20) n (%)	2 to <5 Years (N=20) n (%)	5 to <18 Years (N=32) n (%)	
Safety population	19 (95.0)	19 (95.0)	30 (93.8)	68 (94.4)
MITT population	16 (80.0)	18 (90.0)	30 (93.8)	64 (88.9)
PP population	10 (50.0)	11 (55.0)	19 (59.4)	40 (55.6)
PK population				
Anidulafungin	17 (85.0)	19 (95.0)	30 (93.8)	66 (91.7)
PK sub-study	6 (30.0)	0	0	6 (8.3)
Polysorbate 80	8 (40.0)	0	0	8 (11.1)

Source: Table 14.1.1.1.
Abbreviations: MITT=Modified Intent-to-Treat; N=number of subjects enrolled in the study; n=number of subjects in study population; PK=pharmacokinetics; PP=Per-Protocol.

The CHMP considered that, within the 9 year period this trial ran for, 72 subjects were screened, 70 were included in the study and 68 subjects were treated. Of the 68 subjects who were treated and thus included in the safety population, four were removed from the mITT (primary analysis population) as they did not have confirmation of invasive candida infection. Approximately half of patients who were screened were included in the per protocol population (n=40, 55.6%) reflecting a high rate of protocol deviations which is not surprising considering the patient population (see also above for a discussion of protocol deviations).

Outcomes and estimation

Efficacy was evaluated as a secondary objective with relevant secondary outcomes being Global Response at EOIVT and subsequent time points, relapse rates (2 & 6 weeks follow up), emerging infection rates (2 & 6 weeks follow up) and all-cause mortality. PK and exposure-response are discussed elsewhere in this AR. Subgroup analyses included examination of response data in various categories, including age group, site of infection, *Candida spp*., and neutropenic status.

Global response (combination of clinical and microbiological response as assessed by the Investigator) of success, failure, or indeterminate at the EOIVT and subsequent time points;

An overall global response of success was observed in **45 of 64 (70.3%) subjects at EOIVT.** Over 90% of subjects in the MITT population overall and in each age group had Candida isolated from blood only.

A sensitivity analysis of global response was performed excluding indeterminate and missing data. In this analysis, the success rate overall was 88.2% at EOIVT, 88.5% at EOT, 86.8% at the 2-week follow-up, and 81.1% at the 6-week follow-up.

The Global response of success at EOIVT was 87.5 % (73.2, 95.8) in the PP population.

Global response by age group

Accounting for the small number of subjects, there were no notable trends with respect to global response between age groups. At EOT, the rate of success per age group was similar.

Table 1. Summary of Global Response by Age Group – Modified Intent-to-Treat Population

Time Point	Global Response	Age Group			Overall (N=64) n (%)
		1 Month to <2 Years (N=16) n (%)	2 to <5 Years (N=18) n (%)	5 to <18 Years (N=30) n (%)	
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 FU	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 FU	Success (%)	11 (68.8)	12 (66.7)	20 (66.7)	43 (67.2)
	Exact 95% CI	(41.3, 89.0)	(41.0)	(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)

Global response of success was defined as clinical cure or improvement and microbiologic eradication or presumed eradication.
Exact 95% CI for binomial proportions using Clopper-Pearson method.
Abbreviations: CI=confidence interval; EOIVT=end of intravenous treatment; EOT=end of treatment; FU=follow-up; N=number of subjects in the population; n=number of subjects with responses.
Source: Module 5.3.5.2 Study A8851008 CSR In-Text Table 13

The CHMP noted that the global response rate at end of IV treatment in the overall study population is 70.3% for the MITT population. Response rates are higher in the per protocol population as well as when missing data are disregarded. Response rates are roughly in line with rates seen in adults: in adults with ICC the success rate at EOIVT was 76% (88/116), at 2-week FU it was 65% (82/127), an 6-week FU it as 56% (71/127).

Relapse rate and all-cause mortality

Relapse of infection was reported in 3 subjects at the 6-week follow-up visit. No new *Candida* infections were reported for subjects at the 2- and 6-week follow-up visits.

The overall all-cause mortality rate was 12.5% (8 subjects). While the observed mortality rates were varied between age cohorts, a meaningful interpretation is difficult due to the low number of subjects.

Global Response by site of infection

Blood Only

Overall and across all the 3 age groups, the most common sites of infection were blood (n=61, 95.3%) and catheter site (n=42, 65.6%). Of the 42 subjects with "catheter site" infection, 41 also had an infection site of "blood".

For blood only infections, overall global response success rates at the EOIVT and EOT visits were identical and observed in 42 (71.2%) subjects. Across the 3 age groups, global response success rates at both visits was 9 of 14 (64.3%) subjects in the 1 month to <2 years age group, 13 of 16 (81.3%) subjects in the 2 to <5 years age group, and 20 of 29 (69.0%) subjects in the 5 to <18 years age group.

Overall, 12 (20.3%) subjects had an indeterminate response at both EOIVT and EOT, with relatively similar proportions across all 3 age groups.

Among subjects for whom follow-up clinical and microbiological response assessments were available (n=59), an overall global response rate of success was observed in 42 (71.2%) subjects at the 2-week follow-up, and in 39 (66.1%) subjects at the 6-week follow-up.

Blood and Other Sterile Sites

Two subjects had infections in blood and other sterile sites. The overall global response success rate in this category at all study visits was 50.0%. One subject [redacted] in the 2 to <5 years age group had reported source of infection as blood, eyes, and urinary tract. Though the Investigator assessed this subject as a clinical cure and microbiological eradication at EOIVT, the Sponsor assessed the global response as failure for all study visits because the Investigator discontinued subject's study treatment to begin fluconazole IV for treatment of *Candida albicans* in the urine.

Sterile Sites (Other than Blood Only)

For infections in sterile sites (other than blood only) the overall global response success rate at EOIVT and EOT was 66.7% (2 of 3 subjects) and 100% (3 of 3 subjects), respectively.

Global Response by Candida spp

Global response success rates in the most frequently reported *Candida* spp. are presented in Table 4.

Table 2. Global Response by *Candida* Species and Age Group at End of Intravenous Treatment and End of Treatment (in the most frequently reported *Candida* spp.) - Modified Intent-to-Treat Population

	Age Group						Overall n (%)	
	1 Month to <2 Years, n (%)		2 to <5 Years, n (%)		5 to <18 Years, n (%)			
	EOIVT	EOT	EOIVT	EOT	EOIVT	EOT	EOIVT	EOT
***Candida albicans*, n**	**7**	**7**	**10**	**10**	**8**	**8**	**25**	**25**
Success	4 (57.1)	4 (57.1)	7 (70.0)	7 (70.0)	4 (50.0)	5 (62.5)	15 (60.0)	16 (64.0)
Failure	1 (14.3)	1 (14.3)	1 (10.0)	1 (10.0)	1 (12.5)	1 (12.5)	3 (12.0)	3 (12.0)
Indeterminate	2 (28.6)	2 (28.6)	2 (20.0)	2 (20.0)	3 (37.5)	2 (25.0)	7 (28.0)	6 (24.0)
***Candida parapsilosis*, n**	**5**	**5**	**2**	**2**	**10**	**10**	**17**	**17**
Success	3 (60.0)	3 (60.0)	2 (100)	2 (100)	8 (80.0)	8 (80.0)	13 (76.5)	13 (76.5)
Failure	1 (20.0)	1 (20.0)	0	0	1 (10.0)	1 (10.0)	2 (11.8)	2 (11.8)
Indeterminate	1 (20.0)	1 (20.0)	0	0	1 (10.0)	1 (10.0)	2 (11.8)	2 (11.8)
***Candida tropicalis*, n**	**2**	**2**	**1**	**0**	**6**	**6**	**9**	**9**
Success	2 (100)	2 (100)	1 (100)	1 (100)	2 (33.3)	2 (33.3)	5 (55.6)	5 (55.6)
Failure	0	0	0	0	1 (16.7)	1 (16.7)	1 (11.1)	1 (11.1)
Indeterminate	0	0	0	0	3 (50.0)	3 (50.0)	3 (33.3)	3 (33.3)
***Candida lusitaniae*, n**	**0**	**0**	**1**	**1**	**4**	**4**	**5**	**5**
Success	0	0	1 (100)	1 (100)	4 (100)	4 (100)	5 (100)	5 (100)
Failure	0	0	0	0	0	0	0	0
Indeterminate	0	0	0	0	0	0	0	0

Global response of success was defined as clinical cure or improvement and microbiologic eradication or presumed eradication.
Global response of indeterminate was defined as clinical response of indeterminate and/or microbiological response of indeterminate and neither clinical response of failure nor unsuccessful microbiological response (persistence or new infection or relapse).
Abbreviations: EOIVT=end of intravenous treatment; EOT=end of treatment; n=number of subjects at available for evaluation at time point; MITT=Modified Intent-to-Treat; spp.=species.
Source: Module 5.3.5.2 Study A8851008 CSR In-Text Table 14

The CHMP considered that the failure rates are similar per species, whilst there is some variation in the indeterminates. However, numbers per strata are particularly low, no CIs are given and no conclusions should be drawn.

Global Response by neutropenic status

The overall global response success rate at EOIVT was lower (63.6%) among subjects in the MITT population with laboratory-confirmed neutropenia (ANC ≤500 cells/mm3) at baseline (n=11) compared to those with ANC >500 cells/mm3.

Table 15. Global Response by Baseline Neutrophil Status and Age Group at End of Intravenous Treatment and End of Treatment - Modified Intent-to-Treat Population

Thresh-old	Global Response	Age Group						Overall (N=54)	
		1 Month to <2 Years, (N=13)		2 to <5 Years, (N=16)		5 to <18 Years, (N=25)			
		EOIVT	EOT	EOIVT	EOT	EOIVT	EOT	EOIVT	EOT
ANC ≤500	n	2	2	3	3	6	6	11	11
	Success	2 (100)	2 (100)	2 (66.7)	2 (66.7)	3 (50.0)	3 (50.0)	7 (63.6)	7 (63.6)
	Failure	0	0	0	0	1 (16.7)	1 (16.7)	1 (9.1)	1 (9.1)
	Indeterminate	0	0	1 (33.3)	1 (33.3)	2 (33.3)	2 (33.3)	3 (27.3)	3 (27.3)
ANC >500	n	11	11	13	13	19	19	43	43
	Success	8 (72.7)	8 (72.7)	11 (84.6)	11 (84.6)	14 (73.7)	15 (78.9)	33 (76.7)	34 (79.1)
	Failure	1 (9.1)	1 (9.1)	0	0	2 (10.5)	2 (10.5)	3 (7.0)	3 (7.0)
	Indeterminate	2 (18.2)	2 (18.2)	2 (15.4)	2 (15.4)	3 (15.8)	2 (10.5)	7 (16.3)	6 (14.0)

Source: Table 14.2.32.
Global response of success was defined as clinical cure or improvement and microbiological eradiation or presumed eradication.
Global response of indeterminate was defined as clinical response of indeterminate and/or microbiological response of indeterminate and neither clinical response of failure nor unsuccessful microbiological response (persistence or new infection or relapse).
Analysis includes only subjects for whom an absolute neutrophil count was available at baseline.
Abbreviations: ANC=absolute neutrophil count; EOIVT=end of intravenous treatment; EOT=end of treatment; MITT=Modified Intent-to-Treat; N=number of subjects in the population; n=number of subjects available for evaluation at time point.

The CHMP noted that numbers are low (n=11 vs n=43). Therefore, data should be cautiously interpreted. The success rate is numerically lower in patients with neutropenia at baseline. Failure rates are not dissimilar. However, numbers are low, confidence intervals have not been computed but are expected to be wide.

Clinical cure

An overall clinical response of success (cure plus improvement) was observed in 50 of 64 (78.1%) subjects at EOIVT, and in 49 of 64 (76.6%) subjects at EOT. Across the 3 age groups, a clinical response rate of success ranged from 68.8 to 83.3% at both EOIVT and EOT.

Table 16. Summary of Clinical Response by Age Group at End of Intravenous Treatment and End of Treatment - Modified Intent-to-Treat Population

Response Category	Age Group						Overall (N=64)	
	1 Month to <2 Years, (N=16)		2 to <5 Years, (N=18)		5 to <18 Years, (N=30)			
	EOIVT	EOT	EOIVT	EOT	EOIVT	EOT	EOIVT	EOT
n	16	16	18	18	30	30	64	64
Cure	9 (56.3)	11 (68.8)	11 (61.1)	12 (66.7)	18 (60.0)	21 (70.0)	38 (59.4)	44 (68.8)
Improvement	2 (12.5)	0	4 (22.2)	3 (16.7)	6 (20.0)	2 (6.7)	12 (18.8)	5 (7.8)
Failure	1 (6.3)	1 (6.3)	0	0	1 (3.3)	1 (3.3)	2 (3.1)	2 (3.1)
Indeterminate	4 (25.0)	4 (25.0)	3 (16.7)	3 (16.7)	5 (16.7)	6 (20.0)	12 (18.8)	13 (20.3)

Source: Table 14.2.20.
Investigator's assessment of clinical response. Clinical response of indeterminate was defined as evaluation cannot be made due to withdrawal from the study prior to assessment of cure or failure. Subjects who received fewer than 3 doses of study medication will be assigned as a clinical efficacy response of indeterminate.
Abbreviations: EOIVT=end of intravenous treatment; EOT=end of treatment; MITT=Modified Intent-to-Treat; N=number of subjects in the population; n=number of subjects at available for evaluation at time point.

Microbiological Response

A microbiological response of success (eradication plus presumed eradication) was observed in 54 of 64 (84.4%) subjects at EOIVT and 56 of 64 (87.5%) subjects at EOT.

Table 17. Summary of Microbiological Response by Age Group at End of Intravenous Treatment and End of Treatment - Modified Intent-to-Treat Population

Microbiologic Response	Age Group						Overall (N=64)	
	1 Month to <2 Years (N=16)		2 to <5 Years (N=18)		5 to <18 Years (N=30)			
	EOIVT	EOT	EOIVT	EOT	EOIVT	EOT	EOIVT	EOT
n	16	16	18	18	30	30	64	64
Eradication	12 (75.0)	13 (81.3)	15 (83.3)	13 (72.2)	22 (73.3)	23 (76.7)	49 (76.6)	49 (76.6)
Presumed eradication	1 (6.3)	0	2 (11.1)	4 (22.2)	2 (6.7)	3 (10.0)	5 (7.8)	7 (10.9)
Persistence	2 (12.5)	2 (12.5)	0	0	2 (6.7)	1 (3.3)	4 (6.3)	3 (4.7)
Indeterminate	1 (6.3)	1 (6.3)	1 (5.6)	1 (5.6)	4 (13.3)	3 (10.0)	6 (9.4)	5 (7.8)

Source: Table 14.2.21.
Investigator's assessment of microbiological response. Microbiological response of indeterminate was defined as culture data are not available for a subject with a clinical outcome of indeterminate.
Abbreviations: EOIVT=end of intravenous treatment; EOT=end of treatment; MITT=Modified Intent-to-Treat; N=number of subjects in the population; n=number of subjects at available for evaluation at time point.

The CHMP noted that Clinical Cure and Microbiological response in the MITT is roughly in line with the Global Response.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see below).

Table 1. Summary of Efficacy for trial A8851008

Title: A Prospective, Open-Label Study to Assess the Pharmacokinetics, Safety and Efficacy of Anidulafungin when used to Treat Children with Invasive Candidiasis, including Candidemia			
Study identifier	**A8851008**		
Design	Single arm, prospective multi centre study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		9 years (27/2/09 to 14/2/18) not applicable not applicable
Hypothesis	Exploratory: to describe PK, safety and efficacy		
Treatments groups			anidulafungin IV treatment (3.0 mg/kg loading dose on Study Day 1 followed by 1.5 mg/kg maintenance dose daily thereafter) (n=68)
Endpoints and definitions	Primary endpoint	Safety[1]	safety and tolerability of anidulafungin, when used to treat children with ICC
	Secondary endpoint	Global response	Global response of success, failure, or indeterminate at the EOIVT and subsequent time points
	Secondary endpoint	PK	Pharmacokinetic parameters of anidulafungin in children aged 1 month to <2 years following IV infusion of anidulafungin: AUC24 and Cmax
Database lock			
Results and Analysis			
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Efficacy: - Population: modified intent to treat, subjects who have received at least one dose of study drug and who have microbiological evidence of Candida infection. - Timepoint: End of IV treatment (EOIVT)		
Descriptive statistics and estimate variability	Treatment group		
	Number of subject		N=64
	global response success rates		**70.3%**
	95% CI		**57.6, 81.1**
	Microbiological response at EOIVT		76.6%,
	95% CI		*Not given*
	clinical cure at EOIVT		59.4%
	95% CI		*Not given*
Notes	Global response at EOIVT was higher in the PP population (87.5 % (73.2, 95.8)) and when missing data were discounted. At EOT global response was 71.9%, at 6 week FUP global response was 67.2%.		

1: Safety results are described under the clinical safety section

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This single arm prospective set out to assess the safety, efficacy, and PK of anidulafungin in children 1 month to <18 years of age with ICC. The study would have benefitted from a control arm. Objectives and endpoints, as defined, are considered appropriate.

Inclusion criteria were significantly altered during the course of the study however as only 2 subjects were recruited under the new inclusion criteria, i.e. being at high risk for ICC without microbiologically confirmed ICC, the impact on the conclusions of this study is considered to be minimal.

Subjects received anidulafungin IV treatment with a 3.0 mg/kg loading dose on Study Day 1 followed by 1.5 mg/kg maintenance dose daily thereafter IV for a minimum of 10 days to a maximum of 35 days. There was an option to switch to oral treatment with fluconazole (6 to 12 mg/kg/day, maximum 800 mg/day) after at least 10 days of IV treatment.

Over a 9 year period, 72 patients were screened, 70 were randomised and 68 were treated. Of these, 19 subjects were in the 1 month to <2 years age group, 19 subjects in the 2 to <5 years age group and 30 subjects in the 5 to <18 years age group.

The baseline characteristics of subjects were reflective of a patient population at high risk of ICC with high rates of the central catheter and broad spectrum antibiotic use, total parenteral nutrition, underlying malignancy, and chemotherapy. The most commonly reported baseline pathogens in the MITT population included *Candida albicans* (39.1%), *Candida parapsilosis* (26.6%), and *Candida tropicalis* (14.1%).

Efficacy data and additional analyses

The overall global response success rates in the MITT population at End of IV treatment were **70.3% (95% CI: 57.6, 81.1)** at EOIVT. Success rates were slightly higher in the PP population. Response rates are roughly in line with rates seen in adults: in adults with ICC the success rate at EOIVT was 76% (88/116), at 2-week FU it was 65% (82/127), a 6-week FU it as 56% (71/127).

As over 90% of subjects in the MITT population had Candida isolated from blood only, global response rates in subjects with candidemia (blood only infections) were similar to the overall population at all time points. Success rates at EOIVT were slightly lower (63.6%) in patients with neutropenia at baseline than patients without neutropenia at baseline, however this is based upon 11 subjects only.

2.4.3. Conclusions on the clinical efficacy

Although data are limited, overall the data provided by study A8851008 suggest that the efficacy in paediatric patients aged 1 month to 18 years with ICC can be expected to be largely in line with the efficacy observed in adults.

2.5. Clinical safety

Introduction

In adults, the safety profile of anidulafungin in patients with invasive candidaemia was found to be comparable to fluconazole, with higher rates of respiratory distress and dyspnoe. Infusion-related adverse reactions have been reported with anidulafungin in clinical studies, including rash, pruritus dyspnoea, bronchospasm, hypotension (common events), flushing, hot flush and urticaria (uncommon events).

Increased levels of hepatic enzymes have been seen in healthy subjects and patients treated with anidulafungin. In some patients with serious underlying medical conditions who were receiving multiple concomitant medicines along with anidulafungin, clinically significant hepatic abnormalities have occurred. Cases of significant hepatic dysfunction, hepatitis, and hepatic failure were uncommon in clinical trials. Patients with increased hepatic enzymes during anidulafungin therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing anidulafungin therapy.

Patient exposure

Of the 72 screened subjects, 4 subjects did not receive study drug and were not included in the safety population: the safety population included 19 subjects in the 1 month to <2 years age group, 19 subjects in the 2 to <5 years age group and 30 subjects in the 5 to <18 years age group.

The median duration of anidulafungin treatment for the overall safety population was 11 days. Of the 68 subjects, 31 subjects were switched to receive treatment with fluconazole for a median duration of 8 days. The total median duration of overall treatment (anidulafungin plus fluconazole) was 17 days.

Table 5.5. 1 Treatment Duration - Safety Population (A8851008)

	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.

Adverse events

There were 422 treatment emergent adverse events reported in 66 subjects. A total of 45 treatment-related AEs were reported in 21 (30.9%) subjects. No notable trends were observed across the 3 age groups with regard to overall AEs.

The 3 most commonly reported TEAEs were vomiting (n=16, 23.5%), diarrhoea (n=15, 22.1%), and pyrexia (n=13, 19.1%). The most commonly reported TEAEs reported in the Investigations SOC were increased ALT (n=7, 10.3%), increased AST (n=5, 7.4%), and transaminases increased (n=4, 5.9%).

Table 23. Summary of Treatment-Emergent Adverse Events Experienced by 3 or More Subjects Overall per Preferred Term - Safety Population

SOC and Preferred Term	1 Month to <2 Years n (%)	2 to <5 Years n (%)	5 to <18 Years n (%)	Total n (%)
Number of Subjects:				
Evaluable for TEAEs	19	19	30	68
With TEAEs	17 (89.5)	19 (100)	30 (100)	66 (97.1)
Discontinued due to TEAEs	2 (10.5)	2 (10.5)	3 (10.0)	7 (10.3)
Blood and lymphatic system disorders	10 (52.6)	4 (21.1)	9 (30.0)	23 (33.8)
Anaemia	5 (26.3)	3 (15.8)	1 (3.3)	9 (13.2)
Pancytopenia	2 (10.5)	1 (5.3)	0	3 (4.4)
Thrombocytopenia	2 (10.5)	1 (5.3)	2 (6.7)	5 (7.4)
Thrombocytosis	1 (5.3)	0	2 (6.7)	3 (4.4)
Febrile neutropenia	1 (5.3)	1 (5.3)	3 (10.0)	5 (7.4)
Leukopenia	1 (5.3)	1 (5.3)	1 (3.3)	3 (4.4)
Neutropenia	1 (5.3)	0	3 (10.0)	4 (5.9)
Gastrointestinal disorders	8 (42.1)	8 (42.1)	18 (60.0)	34 (50.0)
Diarrhoea	4 (21.1)	2 (10.5)	9 (30.0)	15 (22.1)
Abdominal distension	0	1 (5.3)	3 (10.0)	4 (5.9)
Abdominal pain	0	3 (15.8)	3 (10.0)	6 (8.8)
Nausea	0	1 (5.3)	3 (10.0)	4 (5.9)
Vomiting	4 (21.1)	7 (36.8)	5 (16.7)	16 (23.5)
General disorders and administration site conditions	6 (31.6)	6 (31.6)	11 (36.7)	23 (33.8)
Pyrexia	4 (21.1)	3 (15.8)	6 (20.0)	13 (19.1)
Hepatobiliary disorders	1 (5.3)	1 (5.3)	3 (10.0)	5 (7.4)
Hyperbilirubinaemia	0	1 (5.3)	2 (6.7)	3 (4.4)
Infections and infestations	13 (68.4)	10 (52.6)	17 (56.7)	40 (58.8)
Staphylococcal bacteraemia	0	3 (15.8)	1 (3.3)	4 (5.9)
Bacteraemia	2 (10.5)	0	1 (3.3)	3 (4.4)
Device related infection	1 (5.3)	2 (10.5)	0	3 (4.4)
Lower respiratory tract infection	1 (5.3)	0	2 (6.7)	3 (4.4)
Pneumonia	1 (5.3)	0	4 (13.3)	5 (7.4)
Sepsis	2 (10.5)	0	1 (3.3)	3 (4.4)
Septic shock	0	1 (5.3)	2 (6.7)	3 (4.4)
Upper respiratory tract infection	1 (5.3)	2 (10.5)	1 (3.3)	4 (5.9)
Investigations	5 (26.3)	6 (31.6)	10 (33.3)	21 (30.9)
Alanine aminotransferase increased	2 (10.5)	2 (10.5)	3 (10.0)	7 (10.3)
Aspartate aminotransferase increased	2 (10.5)	1 (5.3)	2 (6.7)	5 (7.4)
Transaminases increased	1 (5.3)	0	3 (10.0)	4 (5.9)
Metabolism and nutrition disorders	3 (15.8)	6 (31.6)	9 (30.0)	18 (26.5)
Hypocalcaemia	1 (5.3)	1 (5.3)	2 (6.7)	4 (5.9)
Hyponatraemia	0	0	4 (13.3)	4 (5.9)
Hypoglycaemia	1 (5.3)	2 (10.5)	1 (3.3)	4 (5.9)
Hypoproteinaemia	0	2 (10.5)	1 (3.3)	3 (4.4)
Nervous system disorders	1 (5.3)	3 (15.8)	8 (26.7)	12 (17.6)
Headache	0	1 (5.3)	6 (20.0)	7 (10.3)
Seizure	1 (5.3)	1 (5.3)	1 (3.3)	3 (4.4)

Psychiatric disorders	1 (5.3)	4 (21.1)	2 (6.7)	7 (10.3)
Agitation	0	3 (15.8)	1 (3.3)	4 (5.9)
Respiratory, thoracic and mediastinal disorders	5 (26.3)	7 (36.8)	11 (36.7)	23 (33.8)
Epistaxis	1 (5.3)	3 (15.8)	5 (16.7)	9 (13.2)
Skin and subcutaneous tissue disorders	6 (31.6)	6 (31.6)	7 (23.3)	19 (27.9)
Rash	2 (10.5)	2 (10.5)	2 (6.7)	6 (8.8)
Vascular disorders	3 (15.8)	2 (10.5)	6 (20.0)	11 (16.2)
Hypotension	0	2 (10.5)	3 (10.0)	5 (7.4)

Source: Table 14.3.1.2.2.
Subjects were counted only once for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (Version 20.1) coding dictionary applied.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects with event; TEAE=treatment-emergent adverse event.

Overall, 3 (15.8%) subjects in the 1 month to <2 years age group, 4 (21.1%) subjects in the 2 to <5 years age group, and 14 (46.7%) subjects in the 5 to <18 years age group experienced an anidulafungin-related TEAE. While the proportion of TEAEs was higher in the oldest age group; overall, no notable trends were identified between age groups.

The majority of TEAEs were not considered treatment-related; a total of 45 treatment-related TEAEs (attributed to either anidulafungin or fluconazole) were reported in 21 (30.9%) subjects.

The most commonly reported treatment-related TEAEs attributed to anidulafungin were diarrhoea (4 subjects, 5.9%), vomiting, pyrexia, increased ALT, and increased AST (each reported by 3 subjects, 4.4%). With the exception of diarrhoea, vomiting, and pyrexia, no other anidulafungin related TEAEs were reported by more than 1 subject within an age group.

Table 25. Summary of Treatment-Related (Anidulafungin) Treatment-Emergent Adverse Events - Safety Population

System organ class Preferred Term	1 Month to <2 Years (N=19)	2 to <5 Years (N=19)	5 to <18 Years (N=30)	Total (N=68)
Number (%) of subjects with treatment-related AEs	3 (15.8)	4 (21.1)	14 (46.7)	21 (30.9)
Number (%) of subjects discontinued due to AEs	1 (5.3)	2 (10.5)	2 (6.7)	5 (7.4)
Blood and lymphatic system disorders	0	1 (5.3)	2 (6.7)	3 (4.4)
Anaemia	0	1 (5.3)	0	1 (1.5)
Leukopenia	0	1 (5.3)	1 (3.3)	2 (2.9)
Neutropenia	0	0	1 (3.3)	1 (1.5)
Eye disorders	0	1 (5.3)	0	1 (1.5)
Periorbital oedema	0	1 (5.3)	0	1 (1.5)
Gastrointestinal disorders	1 (5.3)	1 (5.3)	6 (20.0)	8 (11.8)
Gastrointestinal haemorrhage	0	0	1 (3.3)	1 (1.5)
Diarrhoea	1 (5.3)	0	3 (10.0)	4 (5.9)
Abdominal pain	0	0	1 (3.3)	1 (1.5)
Nausea	0	0	1 (3.3)	1 (1.5)
Vomiting	0	1 (5.3)	2 (6.7)	3 (4.4)
Salivary hypersecretion	0	0	1 (3.3)	1 (1.5)
General disorders and administration site conditions	1 (5.3)	0	3 (10.0)	4 (5.9)
Catheter site inflammation	0	0	1 (3.3)	1 (1.5)
Pyrexia	1 (5.3)	0	2 (6.7)	3 (4.4)
Chest pain	0	0	1 (3.3)	1 (1.5)
Oedema	0	0	1 (3.3)	1 (1.5)
Infections and infestations	0	0	1 (3.3)	1 (1.5)
Pneumonia	0	0	1 (3.3)	1 (1.5)
Investigations	1 (5.3)	1 (5.3)	3 (10.0)	5 (7.4)
Alanine aminotransferase increased	1 (5.3)	1 (5.3)	1 (3.3)	3 (4.4)
Aspartate aminotransferase increased	1 (5.3)	1 (5.3)	1 (3.3)	3 (4.4)
Liver function test increased	0	0	1 (3.3)	1 (1.5)
Transaminases increased	0	0	1 (3.3)	1 (1.5)
Metabolism and nutrition disorders	0	1 (5.3)	2 (6.7)	3 (4.4)
Hyponatraemia	0	0	1 (3.3)	1 (1.5)
Hypoglycaemia	0	0	1 (3.3)	1 (1.5)
Hypoproteinaemia	0	1 (5.3)	0	1 (1.5)
Musculoskeletal and connective tissue disorders	0	0	2 (6.7)	2 (2.9)
Muscular weakness	0	0	1 (3.3)	1 (1.5)
Myalgia	0	0	1 (3.3)	1 (1.5)
Nervous system disorders	0	0	1 (3.3)	1 (1.5)
Tremor	0	0	1 (3.3)	1 (1.5)
Skin and subcutaneous tissue disorders	1 (5.3)	0	2 (6.7)	3 (4.4)
Erythema	1 (5.3)	0	0	1 (1.5)
Pruritus generalized	0	0	1 (3.3)	1 (1.5)
Rash	0	0	1 (3.3)	1 (1.5)
Skin discolouration	0	0	1 (3.3)	1 (1.5)

Source: Table 14.3.1.3.2.1.
Subjects were counted only once for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (Version 20.1) coding dictionary applied.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects in the population.

A total of 7 (10.3%) subjects discontinued study drug due to AEs; 6 subjects discontinued anidulafungin and 1 subject discontinued fluconazole. Six TEAEs (diarrhea, vomiting, increased ALT, increased AST, generalized pruritus, and increased transaminases), experienced by 5 subjects, were considered by the Investigator to be related to study drug.

All of these resolved with the exception of 1 event of increased transaminases; this event and other hepatobiliary AEs of interest are discussed below. Three TEAEs were considered severe and were also reported as SAEs.

Adverse events of Special Interest

The AEs of special interest for anidulafungin (hepatobiliary events, convulsions, QT prolongation/ Torsades de Pointes, anaphylaxis, infusion-related reactions, and anesthetic exacerbation of infusion-related reactions) were determined in accordance with the anidulafungin risk management plan and the safety review plan. These events were programmatically assessed based on pre-defined standard MedDRA queries (SMQs) and AE PTs (MedDRA, Version 20.1), and are summarized overall in Table 5.

Table 3. Summary of Treatment-Emergent Adverse Events of Special Interest (All Causalities) - Safety Population

	1 Month to <2 Years (N=19)		2 to <5 Years (N=19)		5 to <18 Years (N=30)		Overall (N=68)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Convulsion	1 (5.3)	0.1, 26.0	1 (5.3)	0.1, 26.0	1 (3.3)	0.1, 17.2	3 (4.4)	0.9, 12.4
Hepatobiliary events	4 (21.1)	6.1, 45.6	3 (15.8)	3.4, 39.6	9 (30.0)	14.7, 49.4	16 (23.5)	14.1, 35.4
Anaphylaxis	7 (36.8)	16.3, 61.6	8 (42.1)	20.3, 66.5	9 (30.0)	14.7, 49.4	24 (35.3)	24.1, 47.8
Infusion-associated reactions	1 (5.3)	0.1, 26.0	1 (5.3)	0.1, 26.0	3 (10.0)	2.1, 26.5	5 (7.4)	2.4, 16.3
Anesthetic exacerbation of infusion-associated reaction	0	NA	0	NA	0	NA	0	NA
QTc prolongation	0	NA	0	NA	1 (3.3)	0.1, 17.2	1 (1.5)	0.0, 7.9

95% CI: Using exact method (Clopper-Pearson) based on F-distribution.
Percentages were based on N.
MedDRA (Version 20.1) coding dictionary applied.
Abbreviations: CI=confidence interval; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects enrolled in the study; n=number of subjects with adverse event of special interest; NA=not available
Source: Module 5.3.5.2 Study A8851008 CSR In-Text Table 30

Anaphylaxis

Although the incidence of anaphylaxis appears artificially high, the search criteria, SMQs, broad and narrow (anaphylactic reaction, angioedema), and preferred terms (infusion-related reaction, hot flush, chills, dizziness, feeling hot, and hyperhidrosis), were used to identify cases potentially indicating anaphylaxis. Overall, 24 (35.3%) subjects experienced events potentially indicating anaphylaxis that were reported due to the wide search criteria used to identify all possible events. *Following review of these events, no confirmed cases of anaphylaxis were reported for anidulafungin-treated subjects.*

Hepatobiliary Events

The incidence of hepatobiliary disorder events is summarized in Table 31. Overall, 16 (23.5%) subjects experienced hepatic-related AEs (in the SOCs of Hepatobiliary disorders, Infections and infestations, Investigations, and Metabolism and nutrition disorders). The majority of events were mild to moderate in severity.

Table 31. Incidence of Treatment-Emergent Adverse Events by Adverse Events of Special Interest (Hepatobiliary Events) - Safety Population

System Organ Class Preferred Term	1 Month to <2 Years (N=19) n (%)	2 to <5 Years (N=19) n (%)	5 to <18 Years (N=30) n (%)	Overall (N=68) n (%)
Number (%) of Subjects with at least 1 hepatobiliary AE of special interest	4 (21.1)	3 (15.8)	9 (30.0)	16 (23.5)
Hepatobiliary disorders	1 (5.3)	1 (5.3)	3 (10.0)	5 (7.4)
Cholestasis	1 (5.3)	0	0	1 (1.5)
Hepatitis acute	0	0	1 (3.3)	1 (1.5)
Hepatomegaly	0	1 (5.3)	0	1 (1.5)
Hyperbilirubinaemia	0	1 (5.3)	2 (6.7)	3 (4.4)
Ocular icterus	0	0	1 (3.3)	1 (1.5)
Infections and infestations	0	0	1 (3.3)	1 (1.5)
Liver abscess	0	0	1 (3.3)	1 (1.5)
Investigations	3 (15.8)	3 (15.8)	7 (23.3)	13 (19.1)
Alanine aminotransferase increased	2 (10.5)	2 (10.5)	3 (10.0)	7 (10.3)
Aspartate aminotransferase increased	2 (10.5)	1 (5.3)	2 (6.7)	5 (7.4)
Gamma-glutamyltransferase increased	1 (5.3)	0	1 (3.3)	2 (2.9)
Liver function test abnormal	0	1 (5.3)	0	1 (1.5)
Liver function test increased	0	0	1 (3.3)	1 (1.5)
Prothrombin time prolonged	0	1 (5.3)	0	1 (1.5)
Transaminases increased	1 (5.3)	0	3 (10.0)	4 (5.9)
Metabolism and nutrition disorders	0	0	1 (3.3)	1 (1.5)
Hypoalbuminaemia	0	0	1 (3.3)	1 (1.5)

Source: Table 14.3.1.2.6.3.
Subjects were counted only once in each row.
Includes data up to 30 days after last dose of study drug.
MedDRA (Version 20.1) coding dictionary applied.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects enrolled in the study; n=number of subjects with adverse event of special interest.

Most events were reported in the Investigations SOC; study drug was permanently discontinued for 3 subjects who experienced 4 hepatobiliary events (transaminases increased, ALT increased, and AST increased).

Three subjects were reported to have severe hepatic-related AEs. Increased ALT and AST was assessed as severe for 1 subject in the 1 month to <2 year age group, and hyperbilirubinemia and transaminases increased were assessed as severe for 1 subject each in the 5 to <18 years age group. Of these, one hepatobiliary event (Subject [redacted], see below under SAEs) was reported as an SAE.

The CHMP noted that increased levels of hepatic enzymes were observed in healthy volunteers. Significant hepatic dysfunction including hepatic failure has been observed in clinical trials in adult patients treated with anidulafungin. In the present study, 23.5% of paediatric patients experienced a hepatic related AE which appears to be more frequent than is observed in adults (in adults reported 1/100 to 1/10). The MAH was asked to comment on the seemingly higher frequency of hepatic AEs in paediatric patients.

With their response, rates of hepatobiliary AEs in different SOCs and by PT as reported in the paediatric and adult patient population were provided:

• Cholestasis is listed as "Common", reflecting a frequency in the adult study population (840 subjects) of 1.0%. One paediatric patient was reported with this event, representing 1.5% of the study population.

• ALT increased is listed as "Common" reflecting a frequency in adults of 2.0%. In the paediatric study, 7 patients were reported with this event, representing 10.3% of the population.

• AST increased is listed as "Common" reflecting a frequency in adults of 1.9%. In the paediatric study, 5 patients were reported with this event, representing 7.4% of the population.

• Blood bilirubin increased is listed as "Common" reflecting a frequency in adults of 1.0%. In the paediatric study, 3 patients were reported with this event, representing 4.4% of the population.

• Gamma-glutamyltransferase increased is listed as "Uncommon" reflecting a frequency in adults of 0.8%. In the paediatric study, 2 patients were reported with this event, representing 2.9% of the population.

The MAH also provided a discussion of the hepatobiliary adverse events in the paediatric population as compared to the adult population and highlighted that study A8851008 enrolled only small numbers of patients making assessment of frequencies of adverse events inaccurate. The limited number of paediatric patients included in clinical studies to date is acknowledged. The uncertainties surrounding the frequency of specific events due to this limited number are also acknowledged.

The MAH furthermore provided information on the individual cases of hepatobiliary ADRs which suggests that in several cases at least the events were not related due to lack of temporal relationship or due to values returning to normal whilst still on anidulafungin. This may also be the case, however, for adults.

Based on the above, the CHMP recommended the following wording for Section 4.8:

"The safety of anidulafungin was investigated in 68 paediatric patients (1 month to <18 years) with ICC in a prospective, open-label, non-comparative paediatric study (see section 5.1). The frequencies of certain hepatobiliary adverse events, including "ALT increased" and "AST increased" appeared at a higher frequency (7-10%) in these paediatric patients than has been observed in adults (2%). Due to the limited size of the study this could be due to chance or differences in underlying disease severity."

The Committee agreed that no changes in the frequencies of the hepatic-related ADRs are needed, as the frequency classification would alter for two ADRs, of which one is borderline and the second is based on only 2 cases.

Finally, the CHMP agreed that the benefit-risk profile is also not significantly affected by the hepatic adverse events and remains positive, with significant benefits for paediatric patients and an acceptable risk.

Adverse Events in Paediatric Subjects Enrolled in Other Studies

Adverse events from 2 clinical studies involving paediatric subjects who were administered anidulafungin are summarized below.

Study VER001 (Duke University study)

This was a prospective, open-label, single centre, pharmacokinetic study of anidulafungin in 15 infants (age range 50-451 days) and neonates (age range 2-28 days) less than 24 months of age with suspected serious infection. Subjects received anidulafungin 3 mg/kg loading dose on day 1 of study and 1.5 mg/kg every 24 hours on study days 2-5. The maximum loading dose did not exceed 200 mg and the maintenance dose 100 mg/day

In this study, AEs were experienced by 8 of 15 subjects, including 3 infants and 5 neonates. There was no discernible pattern of toxicity with respect to AE severity, relatedness, toxicity grade, deaths, SAEs, or AEs leading to discontinuation.

Most AEs were mild or moderate in severity. All AEs were considered by the investigator to be unrelated to anidulafungin.

The most commonly reported AE was worsening hyperbilirubinemia (2 subjects). These 2 AEs of hyperbilirubinemia were considered unrelated to anidulafungin and were observed in the infant group. The 2 subjects who experienced hyperbilirubinemia, however, had prior episodes before the start of study drug.

Study VER002-12

Study VER002-12 was a Phase 1/2 study of the safety, tolerance, and pharmacokinetics of anidulafungin; 25 immunocompromised paediatric subjects with neutropenia aged 2 to 17 years (inclusive) were enrolled. This study is described in Section 5.2 Pharmacokinetic properties of the current, approved ECALTA SmPC. AEs were experienced by all subjects. Most AEs were mild to moderate in intensity. Four subjects experienced 6 AEs considered to be possibly or probably related to study drug by investigator attribution. None of these AEs were serious or led to study drug withdrawal. The most common AE, experienced by 11 (44.0%) subjects, was pyrexia. Other common AEs experienced by at least 5 (20.0%) patients were mucosal inflammation, graft versus host disease, and vomiting (6 [24.0%] subjects each) and cough, hypertension, and hypomagnesemia (5 [20.0%] subjects each). Study drug was discontinued in 3 subjects because of AEs, none of which was attributed to study drug by the investigator. There were no drug-related SAEs.

Serious adverse event/deaths/other significant events

Treatment-emergent SAEs were reported in 30 (44.1%) subjects and 3 of these were considered related to study drug anidulafungin.

- Subject [redacted], a [redacted] Asian male with underlying history of acute lymphocytic leukemia and multiple other reported conditions, including thrombocytopenia, experienced an SAE of **gastrointestinal haemorrhage** on Day 15 which was assessed as severe. The subject's last dose of anidulafungin was on Day 12; fluconazole was administered until Day 16. The subject died due to sepsis on Day 18.
- Subject [redacted], a [redacted] male of other race, was treated with anidulafungin from Day 1 to 10, and experienced an AE of severe transaminases increased which was assessed as an SAE. On Day 1, the subject experienced an SAE of severe medulloblastoma disease progression, with documented tumor progression on MRI. During enrolment, multiple AEs were reported, including, among others: bradycardia (Days 2 and 4), pyrexia (Day 2 to 10), tachypnea and respiratory disorder (Day 3 to 4); scrotal edema (Day 5 onward), penile edema (Day 7 onward), and dyspnea (Day 8 to 10, following a tracheostomy on Day 6 to replace endotracheal intubation from Day -2). On Day 10, the subject developed **severe transaminases increased**, which was also considered an SAE and was assessed by the Investigator as related to anidulafungin; this event resulted in permanent discontinuation of study drug. Other AEs reported as of Day 10 included pupil fixed, areflexia, and epistaxis. The subject died on Day 12. The cause of death, as assessed by the Investigator, was attributed to medulloblastoma disease progression.
- Subject [redacted], a [redacted] white female with a prior history of gastrointestinal obstruction, experienced an SAE of **diarrhoea** (Day 1), which was assessed as severe and resulted in discontinuation of study drug. The event was reported as resolved on Day 6. No other SAEs were assessed as related to either anidulafungin or fluconazole treatment. The majority of SAEs reported had an outcome of recovered/resolved.

Deaths

A total of 10 death cases were reported to the Sponsor; 1 occurred during the active treatment phase, 7 occurred during the post-treatment (follow-up) phase, and 2 occurred post-treatment outside of the

safety reporting period (after the 6-week follow-up visit). For the 8 deaths that occurred during the study reporting period, Investigators specified the cause of death on the CRF as related to one of the following: (1) death from infection under study; (2) death unrelated to infection under study, but infection was still current; or (3) death unrelated to infection under study and no evidence of infection at time of death.

None of the deaths were assessed by the Investigator as related to study drug. One death was assessed by the Investigator to be related to the infection under study:

- Subject [redacted], a [redacted] Asian male, discontinued anidulafungin after 1 dose due to a treatment-related AE of pruritus generalized. The subject then started IV fluconazole and later micafungin; the subject died of septic shock on Day 20.

The remaining 7 deaths were assessed as related to other conditions: intracranial hemorrhage, sepsis/septic shock, acute respiratory failure, acute respiratory distress syndrome, progression of medulloblastoma, and multi-organ failure (metachromatic leukodystrophy.

In the 2 subjects with death related to sepsis/septic shock, the Investigators assessed the deaths as unrelated to the infection under study, but infection was still current.

- Subject [redacted], a [redacted] male of other race died of septic shock on Day 1. Septic shock is noted as present medical history at baseline. The causality of death in the CRF is noted as "Other illness-previous septic shock due to neutropenia, which was caused by previous chemotherapy treatment."

Subject [redacted], a [redacted] Asian male, died of sepsis (on Day 18; causality was reported as being related to acute lymphocytic leukemia). The subject's baseline blood culture was positive for *Candida tropicalis*; however, all subsequent blood cultures were negative for *Candida spp*. On Day 16, a blood culture was positive for *Stenotrophomonas maltophilia*.

Laboratory findings

The majority of individual clinically significant laboratory abnormalities were in haematological parameters (eg, neutropenia, differential cell count percentages), which were most often observed in the context of acute illness (eg, sepsis) or underlying malignancy based on clinical review of subjects' medical history.

Clinically significant laboratory abnormalities related to hepatobiliary parameters are described below.

Of the 17 subjects who met laboratory abnormality criteria for AST, 2 subjects [redacted] and [redacted]) had elevated AST values that did not return to baseline or normal range.

Eighteen subjects met laboratory abnormality criteria for ALT. Of these, 1 subject ([redacted]) had elevated ALT values that did not return to baseline or normal range.

- Subject [redacted], a [redacted] Asian male, experienced non-serious AEs of moderate ALT increased and mild AST increased on Day 3. The AEs were considered related to anidulafungin treatment and resolved on Day 16. A non-serious mild AE of hyperbilirubinemia was reported on Day 16, considered unrelated, and was ongoing at the time of the subject's death due to sepsis (on Day 18; causality was reported as being related to acute lymphocytic leukemia).
- Subject [redacted], a [redacted] male of other race, experienced a severe SAE of transaminases increased as discussed above.

Eleven subjects met laboratory abnormality criteria for total bilirubin. Of these, 2 subjects ([redacted]) had elevated values that had not returned to baseline or normal range by the final study visit.

Two subjects ([redacted] and [redacted]) had ALT and AST elevations >10 × ULN during the treatment period which required discontinuation of study drug. AST values in both subjects normalized by the final study visit. One subject ([redacted]) had ALT elevation >10 × ULN during treatment and was discontinued from study drug.

- Subject [redacted], a [redacted] white female, had elevated ALT and AST values at Screening that trended upward until peaking to 1082 IU/L and 840 IU/L, respectively, on Day 4. Non-serious, moderate AEs of ALT increased and AST increased were reported; these AEs were considered related to anidulafungin treatment and the subject was discontinued from study drug. The events were considered resolved on Day 41.
- Subject [redacted], a [redacted] white male, had relevant medical history of ALT increased and AST increased, both present at Screening. On Day 7, ALT and AST for Subject [redacted] sharply increased to 666 IU/L and 664 IU/L, respectively, both values being >11 × ULN. Severe AEs of ALT increased and AST increased were reported; however, the Investigator continued anidulafungin treatment and reported causality related to chemotherapy vincristine plus daunorubicine (cytolytic action on hepatocytes) given prior to Screening. On Day 11, AST had decreased to within normal limits; the associated severe AE improved to moderate on Day 12, and the moderate AE resolved on Day 19. On Day 57, ALT had decreased to within normal limits; the associated severe AE was considered resolved. The subject continued anidulafungin treatment until Day 16 with no further elevation in LFTs.
- Subject [redacted], a [redacted] male of other race, had transaminases in the normal range during the study until a sudden increase of ALT and AST values to 1887 IU/L and 2329 IU/L, respectively, on Day 10. A severe SAE of transaminases increased was reported. The event was considered related to anidulafungin treatment and resulted in discontinuation of study drug on Day 10. This subject died due to medulloblastoma disease progression on Day 12.

A total of 3 subjects met biochemical criteria for Hy's law, according to the laboratory criteria and were assessed for potential Hy's law cases. In all 3 cases, abnormalities were either reported at baseline or a co-morbid medical condition that could possibly account for the abnormal hepatic enzyme values was reported. In 2 of the 3 subjects ([redacted] and [redacted]), the abnormal LFT values were noted at baseline and were attributed to other causes.

- Subject [redacted], a [redacted] white female, had baseline LFT elevations attributed to concomitant medications; ALT, AST, and total bilirubin all improved during the period of treatment with anidulafungin.
- Subject [redacted], a [redacted] white female, had an underlying condition of cholelithiasis, requiring cholecystectomy (surgery had been planned prior to study enrollment).

Subject [redacted], a [redacted] Asian female, had elevations in transaminases and total bilirubin beginning on Day 3; this subject experienced an AE of liver abscess due to candidiasis (disease under study). ALT and AST values both normalized by EOIVT and total bilirubin values improved after Day 7 and normalized by the 6-week follow-up visit.

Discontinuation due to adverse events

In total, seven (10.3%) subjects discontinued due to treatment emergent adverse events. Six subjects discontinued anidulafungin and 1 subject discontinued fluconazole. Six TEAEs (diarrhoea, vomiting, increased ALT, increased AST, generalized pruritus, and increased transaminases), experienced by 5 subjects, were considered by the Investigator to be related to study drug.

All of these resolved with the exception of a severe AE of increased transaminases which is discussed under SAEs.

Post-marketing experience

It is estimated that 801,962 patients were exposed to anidulafungin worldwide since the product was first approved through 15 October 2018.

Table. Post-marketing Patient Exposure by Age Group, Gender, and Region through 15 October 2018

	United States		EU and ROW		Total Worldwide	
Age (years)	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
0-17	0	740	14057	0	14057	740
18-29	741	1750	0	24054	741	25804
30-49	5310	25146	49821	31806	55131	56952
50-64	10243	20347	105,599	113,678	115,843	134,025
65-74	21685	23296	78281	63755	99967	87051
≥75	29181	48330	87381	46761	116,562	95,091
Total	**67161**	**119,607**	**335,139**	**280,054**	**402,300**	**399,662**
Grand Total	**186,768**		**615,193**		**801,962**	

EU= European Union; ROW = Rest of The World.

The MAH estimated that over 800,000 patients have been exposed to anidulafungin. This includes, according to the table above a significant number of children. It was noted that the estimated exposure pattern in males and females for the age groups 0-17 and 18-29 is, however, striking. It is not entirely clear what the source of the imbalance in exposure between males and females is as the unavailability of the gender and age data for the latest AMR metrics would not expected to lead to an imbalance *per se* but rather would result in the data being presented differently, i.e. not by sex. In any case, this does not impact the B/R assessment for this application. Furthermore, the method of calculation for the post-marketing exposure has been accepted in previous assessments of PSURs and is still considered acceptable. Therefore, no further action is warranted.

The MAHs safety database was searched to identify post-marketing (PM) sourced adverse events (AEs) for paediatric patients receiving anidulafungin. Cumulatively, a total of 1127 cases (1638 AEs) were received from spontaneous sources through the cutoff date of 15 October 2018. Among the total PM cases, 32 cases (56 AEs) representing 2.8% of total PM cases involved paediatric patients (less than or equal to 17 years).

The adverse events reported more than once were as follows: 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).

Overall, the cumulative review of PM paediatric cases did not show any new significant safety findings. Based upon routine post-marketing pharmacovigilance monitoring, there are no new emerging safety concerns identified in this dataset.

Table 18. Cases From Spontaneous Sources Involving Paediatric Patients Through 15 October 2018 (N = 32)

Characteristics	Details	No. of cases
Country Where Event Occurred	Chile	6
	Brazil	3
	Bulgaria	3
	Greece	3
	Israel	3
	South Africa	2
	Spain	2
	United States	2
	Australia	1
	Korea, Republic of (South Korea)	1
	Malaysia	1
	Netherlands	1
	Slovakia	1
	Sweden	1
	Thailand	1
	Venezuela, Bolivarian Republic of	1
Medical confirmation[a]	Medically confirmed	29
	Non medically confirmed	3
Case Seriousness	Serious	14
	Nonserious	18
Age Range (n = 26) Min = 12 days Max = 17.0 years Mean = 8.4 years Median = 11.0 years	Less than or equal to 17 years	32
Sex	Female	12
	Male	10
	Unknown	10
Case Outcome	Fatal	2
	Not resolved	1
	Resolved	6
	Resolving	1
	Unknown	22
Patient History	Present	18
	Unknown	14
Co-Suspect Medications	None	29
	Present	3
Concomitant Medications	Present	9
	Unknown	23

a. Medically confirmed cases are cases reported by a healthcare professional defined as a medically-qualified person such as a physician, dentist, pharmacist, nurse, coroner or as otherwise specified by local regulations. Non-medically confirmed cases are reported by a consumer defined as a person who is not a healthcare professional such as a patient, lawyer, friend or relative of a patient or carer.

Cases in Neonates (Aged 0 to 27 Days)

There were 3 cases reported in neonates, 2 of which were serious.

- Serious case #1 ([redacted]): A neonate patient of unspecified age who received anidulafungin at an unknown dosage for Candida infection and experienced on an unknown *date Transaminases increased and Blood bilirubin increased* (clinical outcome: resolved for both the AEs).

After discharge from hospital and anidulafungin treatment ending, the patient reported Pyrexia and White blood cell count decreased (time to events onset and clinical outcome for both the AEs were unknown). Of note before anidulafungin treatment, the patient received amphotericin B for Candida infection and had neutropenia and thrombocytopenia due to the infection.

- Serious case #2 ([redacted]): A premature male neonate ([redacted]) with systemic Candida, who experienced an AE of *Liver function test abnormal* during treatment with anidulafungin (1.5 mg/kg/day, IV) administered for 3 weeks and amphotericin B (co-suspect). On the 10th day of treatment with anidulafungin, blood cultures were negative and clinical and laboratory picture of the neonate was gradually improved.
- The non-serious case ([redacted]) reported the PT Product use issue with no co-reported AEs.

<u>Cases in Infants (Aged 28 Days to 23 Months)</u>

There were 5 cases reported in infants, 2 of which were serious.

- Serious case #1 ([redacted]): An [redacted] female patient who received anidulafungin. The patient had a medical history of hepatic failure and positive Candida results. Since the patient had to be admitted for a liver transplant, she was transferred to the reporter hospital (the date of the liver transplant was unknown). When she was on the 5th day of anidulafungin treatment, she experienced *metabolic acidosis*. Anidulafungin treatment was permanently discontinued on unknown date. Patient recovered from the event 48 hours later.
- Serious case #2 ([redacted]): A [redacted] patient who received anidulafungin on an unknown date and at an unspecified dosage. The patient experienced Oxygen saturation decreased, Tachycardia, Tachypnea, Cyanosis, Pallor, Pigmentation disorder, and Pyrexia on an unspecified date with unknown outcome.
- The 3 non-serious cases reported the PTs Product use issue ([redacted] and [redacted]) and Drug ineffective ([redacted]) with no co-reported events.

Sex	Medical History Co-Suspect Concomitant Medication	Event (PTs) (MEDRA 21.0) S[a] / NS[b]	Medically confirmed ? Yes/No	Case outcome
[redacted] Male	Liver transplant Not reported Not reported	Metabolic acidosis (S)	Yes	Resolved
[redacted] Child Male	Immunodeficiency/Neoplasm malignant Not reported Acyclovir/meropenem/vancomycin	Anaphylactic shock (S)/ Respiratory disorder (S)/ Rash (NS)/Epistaxis (NS)	Yes	Resolved
[redacted] Male	Neoplasm malignant Not reported Isotretinoin	Respiratory disorder (S)/Bronchospasm(S)/Haemodynamic instability (S)	Yes	Unknown
[redacted] [redacted] Male	Not reported Not reported Amikacin/meropenem Acute lymphocytic leukaemia	Angioedema (S)/Respiratory disorder (S)/ Hypertension (S)/ Pyrexia (S)/ Anaphylactic shock (S)	Yes	Unknown
[redacted] [redacted]	Acute lymphocytic leukaemia Not reported	Hypoglycaemia (S)	Yes	Resolved

Female	Not reported			
[redacted] [redacted] Female	Amphotericin B/ azithromycin/ domperidone/gelatin, glycerol, omega-3 marine triglycerides, tocopherol/meropenem/omeprazole/ sertraline/tocopherol/vancomycin/ vitamins	Transaminases increased (S)	Yes	Resolved

Cases in Children (Aged 2 to 11 Years)

There were 15 cases reported in children, 6 of which were serious.

- The 6 serious cases are summarized in Table 19.
- The 9 non-serious cases reported the following PTs with no associated AEs: Drug administered to patient of inappropriate age, Off label use and Product use issue (3 each).

Cases in Adolescents (Aged 12 to 17 Years)

There were 9 cases reported in adolescents, 4 of which were serious.

- The 4 serious cases are displayed in Table 20.
- The 5 non-serious cases reported the following PTs with no associated AEs: Product use issue (4 each) and Product use in unapproved indication (1).

Case ID Age Sex	Medical History Co-Suspect Concomitant Medication	Event (PTs) (MEDRA 21.0) S[a] / NS[b]	Medically confirmed? Yes/No
[redacted] [redacted] Female	Haematological malignancy Not reported Amphotericin B	Brain injury (S)	Yes
[redacted] [redacted] Female	Acute myeloid leukaemia/Aspergillus infection/ Blindness unilateral/Eye disorder/Eyelid oedema/Surgery/Vision blurred Voriconazole/ciprofloxacin/cefepime/amikacin/amphotericin B Not reported	Drug ineffective (S)/Condition aggravated (S)/ Neutropenia (S)	Yes (literature)
[redacted] [redacted]	Candida infection/Hepatic lesion/Hepatosplenic candidiasis/Lung disorder	Paraplegia (S)/Pyrexia (NS)/Rash	Yes

Male	Not reported Amikacin/G-CSF/nystatin/piperacillin sodium, tazobactam sodium/sulfamethoxazole, trimethoprim/vancomycin	(NS)/Abdominal pain (NS)	
[redacted] [redacted] Female	Acute myeloid leukaemia/Bone marrow transplant/Hepatic failure/Neutropenia/Renal failure Not reported Not reported	Dyspnoea (S)/ Pyrexia (S)	Yes

Warnings are included in the SmPC to address the risk of hepatic effects, anaphylactic reactions and infusion-related reactions associated with anidulafungin use.

2.5.1. Discussion on clinical safety

The median duration of anidulafungin treatment for the overall safety population was 11 days. Of the 68 subjects, 31 subjects were switched to receive treatment with fluconazole for a median duration of 8 days. The total median duration of overall treatment (anidulafungin plus fluconazole) was 17 days.

The 3 most commonly reported TEAEs were vomiting (n=16, 23.5%), diarrhoea (n=15, 22.1%), and pyrexia (n=13, 19.1%). Increased ALT and increased AST was reported by 10.3% (n=7) and 7.4% (n=5) of subjects, respectively. A total of 7 (10.3%) subjects discontinued study drug due to AEs. Transaminases increased was reported by 5.9%(n=4) of subjects. The most commonly reported treatment-related TEAEs attributed to anidulafungin were diarrhoea (4 subjects, 5.9%), vomiting, pyrexia, increased ALT, and increased AST (each reported by 3 subjects, 4.4%). In adults too most commonly reported adverse drug reactions include gastrointestinal adverse events including diarrhoea and vomiting. The study was too small to inform adverse reactions occurring less frequently than roughly 1 in 10 paediatric subjects. There were no clear age-related patterns in the safety however, numbers in different age strata are low.

As seen in the adult patient population, a relatively high proportion of subjects reported hepatic related AEs (23.5%) in this paediatric study. Three subjects were reported to have severe hepatic-related AEs. Study drug was permanently discontinued for 3 subjects who experienced 4 hepatobiliary events (transaminases increased, ALT increased, and AST increased). In addition, three subjects experienced either AST or ALT elevations which did not return to baseline or normal range and two subjects experienced increased bilirubin levels that had not returned to baseline/normal levels. Based on the available data, the risk of hepatic AEs appears higher in paediatric patients, the MAH is requested to discuss this and discuss the consequences for the B/R. Also, additional analyses of the relationship between anidulafungin exposure and the occurrence of clinically significant abnormalities in relation to hepatobiliary parameters and between exposure and the occurrence of treatment-emergent increases in hepatic enzymes were provided (see section 2.3.5).

Treatment-emergent SAEs were reported in 30 (44.1%) subjects. There were 3 SAEs considered related to study drug anidulafungin (gastrointestinal haemorrhage, hepatic enzymes increased, diarrhoea); there

were 10 deaths of which none were considered related to treatment, and one was considered related to ICC.

2.5.2. Conclusions on clinical safety

Although limited, the data provided by study A8851008 suggest that the safety in paediatric patients aged 1 month to 18 years with ICC is largely in line with the safety profile seen in adults, with some indication that there may be increased hepatobiliary adverse reactions. Adequate wording has been added to Section 4.8 of the SmPC to inform prescribers about this.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 13.0 (data lock point 15 October 2018, dated 08 March 2019) with this application for requesting the extended indication to paediatric patients ≥ 1 month of age following completion of study A8851008 (EMEA/H/000788/P46/046). The list of safety concerns were revised based on study A8851008 completion and in line with the GVP Module V (Rev. 2) and the accompanying RMP template (Rev.2.0.1). A summary of the most significant changes in this RMP follows:

RMP Part/Module	Major change(s)
PART I Product Overview	Indication and posology updated to reflect the proposed extension for use in individuals from the age of 1 month
PART II Safety Specification	
Module SI Epidemiology of the indications and target populations	Updated to include paediatric epidemiological data
Module SII Non-clinical part of the safety specification	Revised and aligned with the GVP Module Rev 2 requirements
Module SIII Clinical trial exposure	Updated to data lock point 15 October 2018. Presentation of paediatric exposure data (studies A8851008 and VER002-12)
Module SIV Populations not studied in clinical trials	Updated based on new data available following completion of study A8851008 and aligned with the GVP Module Rev 2 requirements
Module SV post-authorisation experience	Aligned with the GVP Module Rev 2 requirements. The post-authorisation exposure was updated
Module SVI Additional EU requirements for the safety specification	Aligned with the GVP Module Rev 2 requirements

RMP Part/Module	Major change(s)
Module SVII Identified and potential risks	Reclassification of the safety concerns in line with the GVP Module Rev 2 and following completion of study A8851008
Module SVIII Summary of safety concerns	The list of safety concerns has been updated based on the reclassification presented in Module SVII
PART III Pharmacovigilance Plan (including Post Authorisation Safety Studies)	No major changes. Aligned to the current GVP Module V Rev 2
PART IV Plans for Post Authorisation Efficacy Studies	Alignment with the GVP Module V Rev 2 requirements
PART V Risk Minimisation Measures (including evaluation of the effectiveness of risk minimisation activities)	Updated according to changes made to the safety concerns in Module VII
PART VI Summary of the Risk Management Plan	The text has been updated as per current template accompanying GVP Module V Rev 2
PART VII Annexes to the Risk Management Plan	The Annexes have been revised to match the current template accompanying GVP Module V Rev 2

The (main) proposed RMP changes were the following:

PART II SAFETY SPECIFICATION

Module SVII Identified and potential risks

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table xx Safety concerns considered important for inclusion in the list of safety concerns in the RMP (newly added indicated in blue font)

Risks and missing information	Risk-benefit impact
Important potential risks	
Hepatic impairment and other serious toxicities in neonates < 1 month of age	Given the potential risk of hepatotoxicity associated with polysorbate 80 when an increased amount is used in neonates, there is a theoretical risk of additive or synergistic hepatic effects in neonates when exposed to anidulafungin and polysorbate 80 at higher doses. Neonatal exposure to an increased amount of polysorbate 80 in addition to an increased dose of anidulafungin resulted from the clinical need to use higher doses of anidulafungin to cover documented or suspected Candida meningitis. The proposed label includes a warning about the treatment with anidulafungin in neonates (<1 month old).
Missing information	
Pregnant women	Pregnant women were excluded from the clinical studies. There are no adequate or well-controlled data regarding the use of anidulafungin in pregnant women. Studies in animals have shown reproductive toxicity. Therefore, the product label advises that anidulafungin is not recommended during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.
Resistance	The efficacy of anidulafungin can be limited against certain species of fungi. Patients with resistant forms of infection may fail to respond to therapy. No indication from the community or the clinical setting that warrants change to the use of anidulafungin when used appropriately as prescribed in the label. Emerging antifungal resistance will continue to be kept under close surveillance.

SVII.2. New safety concerns and reclassification with a submission of an updated RMP

The MAH proposed to reclassify the **important identified risks** 'Anaphylaxis and Infusion-associated reactions', 'Hepatobiliary events' and 'Convulsions' as identified risks that are not considered important for inclusion in the RMP, in accordance with GVP Module V (Rev 2), and therefore to remove from the list of safety concerns. The rationales (summarized) for the proposed changes to the list of safety concerns are briefly presented below.

The MAH proposed to reclassify the **important potential risks** 'Exacerbation of Infusion-associated reactions by anaesthetics' and 'QT Prolongation/Torsade de Pointes' as potential risks that are not considered important for inclusion in the RMP, therefore to remove from the list of safety concerns.

The MAH proposed to remove the **Missing Information** (MI) 'Children/Adolescents' and to add the important potential risk 'Hepatic impairment and other serious toxicities in neonates < 1 month of age'

based on the completion of Study A8851008. In addition, the missing information 'Elderly' is proposed for removal from the list of safety concerns in accordance with GVP Module V (Rev 2).

Important Identified Risks removed from the List of Safety Concerns

Anaphylaxis and Infusion-associated reactions

The MAH considerd it is an adverse reaction already well-known to health professionals, the event does not require additional pharmacovigilance activities or additional risk minimisation measures, and it has no impact on public health. The SmPC (section 4.2) provides instruction to minimize the potential for infusion-associated reactions. In addition, after over 12 years of post-marketing experience, no significant safety issues have been identified.

Hepatobiliary events

The MAH reclassified this risk as not important as it does not require additional pharmacovigilance activities or additional risk minimisation measures. Monitoring of liver function tests (LFTs) is considered part of standard clinical practice in the patient population likely to receive anidulafungin given the indication (ICC [Invasive Candidiasis/Candidaemia]) and the risk factors for ICC. SmPC section 4.4 recommends dosage adjustments if LFTs worsen during treatment.

Convulsions

The MAH reclassified this risk as not important as it does not require additional pharmacovigilance activities or additional risk minimisation measures, and it has a low impact on public health.

Important Potential Risks removed from the List of Safety Concerns

Exacerbation of Infusion-associated reactions by anaesthetics

The MAH reclassified this risk as not important as it does not require additional pharmacovigilance activities or additional risk minimisation measures, and it has a low impact on public health. No cases were identified in the clinical programme or in the safety database after 12 years of post-marketing experience.

QT Prolongation/Torsade de Pointes

The MAH reclassified this risk as not important as it does not require additional pharmacovigilance activities or additional risk minimisation measures, and it has a low impact on public health. After 12 years of post-marketing experience no safety issues concerning this risk have been identified.

The MAH's proposal to remove the important *identified* risks 'Anaphylaxis and Infusion-associated reactions', 'Hepatobiliary events' and 'Convulsions' from the summary of safety concerns as well as the rationales for the proposed changes was endorsed by the PRAC. Routine risk minimisation measures are in place to sufficiently address the risks of 'Anaphylaxis and Infusion-associated reactions' and 'Hepatobiliary events'. 'Convulsion' is included as an adverse drug reaction in SmPC section 4.8. In addition, routine pharmacovigilance is sufficient to further characterise these risks.

The MAH's proposal to remove the important *potential* risks 'Exacerbation of Infusion-associated reactions by anaesthetics' and 'QT Prolongation/Torsade de Pointes' from the summary of safety concerns was endorsed. In the last PSUSA (EMEA/H/C/PSUSA/00000215/201701), covering the period 01 February 2014 to 31 January 2017, no cases concerning the risks 'Exacerbation of infusion-associated reactions by anaesthetics', and 'QT prolongation/Torsade de Pointes' were received. Routine pharmacovigilance is sufficient to characterise these risks.

Important Potential Risks added to the List of Safety Concerns

Hepatic impairment and other serious toxicities in neonates (< 1 month of age)

The MAH considers the classification of 'children/adolescents' as missing information is no longer appropriate based on the availability of new data following completion of study A8851008. Neonates under 1 month of age have been excluded from the clinical program as the use of anidulafungin in this population may present a different safety profile and therefore warrant remaining among the safety concerns. Therefore, the MAH proposed to add the important potential risk 'Hepatic impairment and other serious toxicities in neonates < 1 month of age' because of potential toxicity of the excipient polysorbate 80 (PS80) resulting from the higher doses that would be needed for the treatment of invasive candidiasis with CNS involvement in this patient population.

The MAH's proposal to add the important potential risk 'Hepatic impairment and other serious toxicities in neonates < 1 month of age' was endorsed by the PRAC. Anidulafungin is indicated in paediatric patients from 1 month of age, however, a potential different safety profile can be expected in this potential target population due to higher doses. A warning for treatment with the product in neonates (<1 month old) is included in SmPC section 4.4. In addition, routine pharmacovigilance is considered sufficient to further characterize this risk in this patient population.

Missing information removed from the List of Safety Concerns

Children/Adolescents

The MAH proposes to remove 'Children/Adolescents' classified as missing information based on completion of study A8851008. Safety data is available from this study and include 68 patients between the ages of 1 month and < 18 years. Overall, the adverse events (AEs) reported were in line with the known safety profile of anidulafungin or the pattern of events expected for the patient population. No new safety concerns were identified in this patient population.

Elderly

The MAH proposes to remove 'Elderly' classified as missing information because there is no evidence that the safety profile in this population would differ from the known safety profile of the product. No additional pharmacovigilance activities or additional risk minimisation measures are required.

The MAH proposes the following safety concerns remain as Missing information:

Pregnant women

Pregnant women were excluded from the clinical studies. There is limited post-marketing experience in pregnant women. There are no adequate or well-controlled data regarding the use of anidulafungin in pregnant women. Foetal toxicity may be experienced if pregnant women are treated with anidulafungin.

Resistance

The efficacy of anidulafungin can be limited against certain species of fungi. Patients with resistant forms of infection may fail to respond to therapy.

The MAH's proposal to remove 'Children/Adolescents' and 'Elderly' classified as missing information was agreed upon by the PRAC. The limited data provided by study A8851008 suggests that the safety profile of the product in the paediatric population is largely in line with the safety profile of anidulafungin in adults, although some clarifications are needed before this conclusion can be conclusively drawn, and/or the events are considered to be related to the underlying disease. In the last PSUSA, covering the period 01 February 2014 to 31 January 2017, no new safety information was identified by evaluation of post-marketing data for use of the product in elderly.

The MAH's proposal to keep 'Pregnant women' and 'Resistance' as missing information was **not** endorsed.

SmPC section 4.6 currently states that Anidulafungin is not recommended during pregnancy unless the benefit to the mother clearly outweighs the potential risks to the foetus which routine risk minimisation measure is considered sufficient. In addition, routine pharmacovigilance is sufficient to identify and characterise this risk.

Resistance constitutes an efficacy concern, not a safety concern, and should therefore be removed from the summary of safety concerns. Trends and patterns in Resistance should continue to be monitored in PSURs.

Accordingly, the MAH submitted the updated RMP version 13.1, with DLP of 15 October 2018 and date of final sign off of 3 December 2019, in which "Pregnant women" and "Resistance" were removed from the list of safety concerns:

Module SVIII Summary of the Safety Concerns

Summary of the Safety Concerns

Summary of Safety Concerns	
Important identified risks	~~Anaphylaxis and IARs~~ ~~Hepatobiliary events~~ ~~Convulsions~~
Important potential risks	~~Exacerbation of IARs by anaesthetics~~ ~~QT prolongation/Torsades de Pointes~~ Hepatic impairment and other serious toxicities in neonates < 1 month of age
Missing information	~~Children/adolescents~~ ~~Elderly~~ ~~Pregnant women~~ ~~Resistance~~

The summary of safety concerns as listed in the updated RMP version 13.1 was acceptable to the PRAC.

PART III PHARMACOVIGILANCE PLAN

There are no ongoing and planned category 1-2 studies for Ecalta. Study A8851008 has been completed since last RMP submission. There are no planned category 3 studies.

The PRAC considered that Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no post-authorization efficacy studies (PAES) that are a specific obligation by the competent authorities and/or condition of the MA.

The PRAC noted the above and agreed. Notably, in the previously approved RMP (version 12.1), study A8851008 was included as a PAES in the RMP.

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE

EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

The product information and labelling (SmPC) submitted within this application is updated based on the data from Study A8851008 and is expected to be sufficient for risk minimisation for all safety concerns.

The MAH states that routine risk minimisation activities are sufficient to manage the safety concerns of Ecalta. No additional risk minimisation measures are proposed.

The PRAC considered that the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.7. Overall conclusion on the RMP

The changes to the RMP are acceptable. Version 13.1 is being approved with this procedure.

2.8. Update of the Product information

As a result of this new indication, section 4.1 of the SmPC is being updated to reflect the experience and recommendations for use in paediatric patients.

Consequently, sections 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated in order to add paediatric dosing instructions, warnings and precautions, clinical, and non-clinical information.

The Package Leaflet (PL) is updated accordingly.

Changes are also made to the PI to bring it in line with the current excipient's guideline for fructose.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.8.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Invasive candidiasis mostly affects critically ill and immunocompromised patients. Candidemia is the most common form of invasive candidiasis and is a leading cause of invasive fungal infections in hospitalized children. Immunosuppressed children, children in intensive care units, children with central venous catheters, and neonates are most at risk for the development of candidemia.

The most prevalent *Candida spp* isolated from patients as infectious agents include *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei*. During the past 10 years, *C. auris* has become increasingly important as isolates cause serious infections, are often multidrug resistant, can be associated with outbreaks in health care facilities, and can be misidentified. The distribution of *Candida spp* causing invasive candidiasis varies geographically and temporally, but also can vary by age. Large

international collaborative studies which assessed the distribution of fungal pathogens in children found a predominance of non-albicans *Candida spp* in paediatric (56%) and neonatal (52%) patients (Warris et al. Curr Fungal Infect Rep 2016; 10:7–9.). Whilst *C. parapsilosis* causes 30% of the candidemia cases among newborns the rate in adults is 10%–15% (Yapar, Ther Clin Risk Manag. 2014; 10: 95–105).

Incidence rates for *Candida spp.* vary according to study design and reporting methods: 0.06 to 0.3 per 1000 inpatient-days (median age: 50 months) in a case-control study; 0.28 per 1000 patient-days in another case-control study in premature infants and children up to age 17 years; and 0.81 per 1000 admissions in a prospective surveillance study.

A decline in paediatric candidemia in Europe and the US during the last decade has been reported (Walsh et al, 2019, J. Fungi 2019, 5, 11; doi:10.3390/jof5010011; Pana et al. Journal of the Paediatric Infectious Diseases Society 2017;6(S1):S3–11).

Mortality for paediatric candidemia is estimated at 22% in the USA, with the highest mortality in paediatrics related to *Candida albicans* at 29%. In older children mortality rates range from 10% to 25% in most reports and reach higher rates in patients admitted to the PICU.

3.1.2. Available therapies and unmet medical need

Current approved treatments for infections due to Candida spp. include echinocandins, polyenes, and the azole antifungal agents. The Infectious Disease Society of America and European Society of Clinical Microbiology and Infectious Diseases guidelines for the prevention and treatment of IC in children primarily rely on extrapolation from adult studies, as safety and efficacy data for antifungal agents in paediatric patients are lacking. According to these guidelines, the first choice treatment for candidemia or (suspected) candidiasis is either an echinocandin or lipid formulation of amphotericin B, with fluconazole or voriconazole as an alternative. Transition from an echinocandin to fluconazole (usually within 5–7 days) is recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (e.g.: *C. albicans*), and have negative repeat blood cultures following initiation of antifungal therapy.

In Europe, caspofungin acetate is indicated for 12 months of age and older, as safety and efficacy of caspofungin have not been sufficiently studied in clinical trials involving neonates and infants below 12 months of age, caution is advised when treating this age group. Micafungin is indicated for children (including neonates) and adolescents 16 years of age and older.

In contrast to anidulafungin, all other available treatments (caspofungin acetate, micafungin sodium, amphotericin B, azoles) have clinically relevant drug-drug interactions that require either monitoring and/or dosing adjustments, some require dosing adjustments for moderate hepatic impairment (caspofungin) or renal insufficiency (fluconazole), and some are associated with clinically important effects such as nephrotoxicity (amphotericin B formulations).

3.1.3. Main clinical studies

The main evidence submitted comes from a population PK/PD analysis and two clinical studies, a small phase I study (Duke IIR Study) evaluating the PK of anidulafungin in infants (n=6) and neonates (n=8) and a prospective, single arm study (A8851008) which evaluated the PK, safety and efficacy of anidulafungin when used to treat children (n=68) with invasive Candidiasis, including Candidemia.

3.2. Favourable effects

The overall evaluation of these exposure data indicates that the currently proposed IV dosing regimen (a 3.0 mg/kg [not to exceed the 200 mg adult dose] LD followed by 1.5 mg/kg [not to exceed the 100 mg adult dose] MD QD) is appropriate for use across all paediatric and adolescent age groups (1 month to <18 years old) since the anidulafungin exposures achieved are comparable to those in adults at the recommended dosing regimen (200 mg LD/100 mg MD QD).

The overall global response success rate observed in Study A8851008, which is a combination of clinical and microbiological response as assessed by the Investigator, in the MITT population at end of IV treatment were 70.3% (95% CI: 57.6, 81.1). At EOT this was 71.9%, with a failure rate of 9.4% (n=6) and at 6 weeks follow up this was 67.2%, with a failure rate of 15.6% (n=10). The Global response of success at EOIVT was 87.5 % (73.2, 95.8) in the PP population. Microbiological response at EOIVT and EOT was slightly higher (76.6%, 49/64 at both timepoints) than the clinical cure at EOIVT (59.4%, 38/64) and EOT (68.8%, 44/64).

3.3. Uncertainties and limitations about favourable effects

The popPK analysis indicated that the proposed IV dosing regimen for paediatric subjects would result in a comparable exposure to that in adults. However, in the individual studies the differences in exposure in paediatrics and adults appeared to be much more pronounced. This should be clarified

Study A8851008 was a descriptive, single-arm study and was open-label limiting potential inference regarding efficacy and safety.

Recruitment spanned nine years, and it is likely that patients recruited in earlier years are no longer comparable to patients recruited in later years as the epidemiology of ICC might have changed but also the treatment of critically ill paediatric patients or immunocompromised patients potentially changing the risks of ICC or the response to treatment as a whole. This also limits the comparison of response rates from Study A8851008 to studies conducted in adults, for example VER002-9.

Study A8851008 included only few subjects, therefore, there is uncertainty surrounding obtained estimates reflected by the wide CI around the primary estimates. Due to the limited number of subjects, assessments of effects in subgroups (i.e. by age, by neutropenic status) are highly uncertain. The use of other antifungal treatments within the studies needs to be clarified, as it is unclear what role other antifungal agents have in relation to the responses seen.

No clear relationships between anidulafungin exposure parameters and efficacy were identified in paediatric and adult subjects with ICC.

3.4. Unfavourable effects

The most commonly reported all-causality AEs were vomiting (n=16, 23.5%), diarrhoea (n=15, 22.1%), and pyrexia (n=13, 19.1%). The most commonly reported laboratory-related all-causality AEs were increased ALT, increased AST, and transaminases increased. Increased ALT and increased AST was reported by 10.3% (n=7) and 7.4% (n=5) of subjects respectively. Transaminases increased was reported by 5.9%(n=4) of subjects. In total, 23.5% of subjects reported hepatic related AEs in this paediatric study.

Overall, no new safety findings were identified for anidulafungin with regard to reported AEs, laboratory safety assessments, physical examinations, or vital signs assessments.

3.5. Uncertainties and limitations about unfavourable effects

Safety and tolerability conclusions should be interpreted with caution due to the small sample size. The study was too small to inform adverse reactions occuring less frequently than roughly 1 in 10 paediatric subjects. Although there were no clear age related patterns in the safety numbers in different age strata are low and firm conclusions can not be drawn. Further, it is unclear whether the hepatic safety is similar or worse as seen in adults.

There was no clear response between exposures and safety parameters, namely GI related adverse events such as vomiting and diarrhoea and hepatic adverse events. Additional analyses were provided to elucidate the relationship between exposure and occurrence of hepatic adverse events. Hepatic adverse drug reactions need to be considered when deciding whether to prescribe anidulafungin to paediatric patients. Wording has been included in Section 4.8 of the SmPC to inform physicians about this.

3.6. Effects Table

Table 2. Effects Table for Anidulafungin for ICC in paediatric patients aged 1 month to 18 years

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Anidulafungin exposures achieved in paediatric patients aged 1 to 18 years with the current proposed IV dose regimen (a 3.0 mg/kg [not to exceed 200 mg] LD followed by 1.5 mg/kg [not to exceed 100 mg] MD QD) are comparable to those in adults at the recommended dosing regimen						
Global response	combination of clinical and microbiological response as assessed by the Investigator, in the MITT population at end of IV treatment	%	70.3	-	*Small non comparative study, lengthy recruitment,* *(95% CI: 57.6, 81.1).*	CSR A8851008,
Unfavourable Effects						
GI safety	vomiting diarrhoea	%	23.5 22.1	-	Limited number of subjects (n=68) to base safety assessment on	CSR A8851008
Hepatic safety	hepatic related AEs	%	23.5	-	See above	CSR A8851008

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Despite the availability of antifungal therapies, including echinocandins, for the treatment of ICC in children, there is still a need for licensed, effective treatments in children. As anidulafungin does not rely on enzymatic degradation or hepatic or renal excretion, the drug is safe to use in patients with any degree of hepatic or renal impairment, and there are limited drug-drug-interactions of clinical relevance. This makes it a potentially welcome addition to the currently available treatments.

As the exposure in paediatric patients aged 1 month to 18 years is comparable to that in adults, anidulafungin can be used in paediatric patients. The small, single-arm clinical study A8851008 confirmed efficacy of anidulafungin as the global response at EOIVT was 70%, similar as what has been seen in

adults. Although the study was limited in size, lacked a comparator arm and recruited over 9 years, making the possibility of inference limited, the comparable efficacy observed in this study is reassuring and supports the extrapolation exercise based on exposure levels in adults and children. Diarrhoea and vomiting were reported very commonly in these paediatric patients, similar if not more frequent as in adults.

Additionally, AEs in the SOC of Hepatobiliary disorders were reported very commonly too (23.5%), which would appear more frequent than in adults. However, this is based upon limited numbers and it is not clear whether underlying comorbidities were similar between the paediatric patients and adult patient population. Whilst increased levels of hepatic enzymes were mostly reversible, three subjects were permanently discontinued from study drug and for three subjects levels did not return to baseline/normal levels by end of study. The hepatic adverse drug reactions are serious and need to be considered by physicians when deciding whether to prescribe anidulafungin to paediatric patients.

3.7.2. Balance of benefits and risks

The balance of benefits and risks of anidulafungin in treating ICC in paediatric patients aged 1 month to 18 years is considered positive.

3.8. Conclusions

The overall B/R of ECALTA is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of the approved indication "treatment of invasive candidiasis (ICC)" to include paediatric patients aged from 1 month to less than 18 years of age; consequently, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated in order to add paediatric dosing instructions, warnings and precautions, clinical, and non-clinical information. The Package Leaflet is updated accordingly consequent to the revisions to the SmPC. In addition, the Marketing Authorisation Holder (MAH) has taken the opportunity to update the information in the SmPC and Package Leaflet in line with the current excipient's guideline for fructose.
The RMP Version number 13.1 was approved.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (P/0053/2017 of 17 March 2017) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Ecalta-H-C-0788-II-0040'