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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

ECALTA

anidulafungin

Procedure no: EMEA/H/C/000788/P46/046

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Introduction

On 28th September 2018, the MAH submitted a completed paediatric study for Ecalta, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended. These data are also submitted as part of the post-authorisation measure (Follow Up Measure 021). A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that 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' is part of a clinical development program.

The variation application consisting of the full relevant data package (i.e. containing PK/PD data from several studies) is expected to be submitted by end of February 2019.

Assessor's comments

The present study will be submitted in an upcoming type II variation application in which the MAH intends to extend the indication and include relevant paediatric data in the labelling. A preliminary assessment of study A8851008 is contained in the current assessment report.

2.2. Information on the pharmaceutical formulation used in the study

All subjects received IV anidulafungin as study drug.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- 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

2.3.2. Pharmacokinetics

Study design

Study A8851008 was a prospective, open-label, non-comparative, multi-centre, multinational study designed to assess the safety, efficacy, and pharmacokinetics (PK) of anidulafungin for the treatment of invasive candidiasis/candidaemia (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 centres. 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 of the following time points during the study for all study subjects, with the exception of subjects in the PK sub-study:

- day 1: post-dose (between 0 and 2 hours following the end of anidulafungin infusion)
- day 3: pre-dose (just prior to the start of anidulafungin infusion)
- day 5: post-dose (between 0 and 3 hours following the end of anidulafungin infusion)
- day 7: delayed post-dose (between 6 and 12 hours following the end of anidulafungin infusion)
- day 9: pre-dose (just prior to the start of anidulafungin infusion)

Assessor's comments

In general the design of the pharmacokinetic part of study A8851008 is acceptable.

Bioanalytical methods

The plasma samples were analysed 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.

Assessor's comments

The bioanalytical methods for both anidulafungin and polysorbate 80 are acceptable.

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 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 summarised in the table below.

Table 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: CV%=percent coefficient of variation; NA=not applicable; PK=pharmacokinetic
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.

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, which supports dose selection for the youngest age group.

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 analysed in a population PK analysis to be reported separately. 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, a 20-month old white male weighing 13 kg, had one sample collected 5 hours post infusion on Day 1 which 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 PK/PD analyses in support of the PK/PD objective will be described in a separate report.

Anidulafungin PK data collected in this study were combined with external PK data across other age groups, including neonates, adults and elderly, and will be reported separately in a comprehensive population PK/PD analysis.

Assessor's comments

Conclusions on the results of pharmacokinetic characterisation are agreed upon.

Discussion on pharmacokinetics

Regarding the pharmacokinetics of anidulafungin, the only results relevant to be discussed at this point are the results of the PK-sub study. Additional population pharmacokinetic model analyses (based on the pharmacokinetic sparse sampling of the full pharmacokinetic dataset including 253 anidulafungin plasma samples from 60 subjects) are still awaited and said to be presented in a separate report, at a later stage.

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 adult population, which supports the chosen dose regimen.

This is agreed. Pharmacokinetics of anidulafungin seem to have been characterised 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 exposures similar to those observed in the adult population. An AUC_{0-24} 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) C_{max} was about 7.2 µg/ml and AUC_{ss} 110 µg.h/ml. It is noted that the observed AUC is somewhat lower in the young age group, and the calculated AUC was

not based on measurements from steady state conditions. Nevertheless, the results do demonstrate an exposure in the youngest age group compared to adult patients which is in the same range and therefore support appropriateness of the dosing regimen of 3.0 mg/kg loading followed by 1.5 mg/kg maintenance the next day.

However, in order to fully assess the pharmacokinetic behaviour of anidulafungin in the paediatric population, the awaited pharmacokinetic modelling is pivotal. Until then, no firm conclusions can be drawn.

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. Clinical 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

Description

This prospective, open label study had the purpose to assess the safety, efficacy, and PK of anidulafungin in children 1 month to <18 years of age with Invasive Candidiasis, including Candidaemia.

Methods

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 (AUC_{24}) and maximum plasma concentration (C_{max}).
- To explore PK parameters of polysorbate 80 following IV infusion of anidulafungin AUC_{24} and C_{max}.
- To explore the exposure-response (safety and efficacy endpoints) relationship of anidulafungin using a nonlinear mixed effects approach as appropriate, including exploring the association between the PK/pharmacodynamic (PD) index, e.g. 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.

Study design

Study A8851008 was a prospective, open-label, non-comparative, multi-centre, 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.

Assessor's comments

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

Study population /Sample size

Assessor's comments

The in- 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 must 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/candidaemia (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/candidaemia (ICC) (all age groups) is based on the growth of *Candida spp*. from a blood and/or tissue culture obtained from a normally sterile site.

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

Microbiologic Criteria:

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

- Candidaemia: At least one blood culture positive for *Candida spp*. (in the absence of other demonstrated foci of infection) or;

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

Clinical Criteria:

1. 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 candidaemia/invasive candidiasis, which may include the following: feeding intolerance, bloody stools, abdominal distension, thrombocytopenia, lethargy, colour change, hyperglycaemia, 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 spp*. (e.g., the growth of yeast in culture and/or the direct microscopic visualisation of yeast, hyphae, or pseudohyphae) from a sample obtained from a normally sterile site (e.g. blood and/or tissue). If culture confirmation of *Candida spp*. 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 spp*. 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/candidaemia. 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 non-absorbable azoles (e.g., 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.

Assessor's comments

In and exclusion criteria have 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 at the EMA. 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.

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: AUC_{24} and C_{max};
- Exposure-response (efficacy and safety endpoints) relationships of anidulafungin using a nonlinear mixed effects approach as appropriate;
- Rates of relapse 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 categorised 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 categorised 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 categorised 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".

Assessor's comments

Primary and secondary outcomes are considered appropriate.

Statistical Methods

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

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

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

Results

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)			
	PDs	n (%)	PDs	n (%)	PDs	n (%)	PDs	n (%)
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						Overall (N=72)	
	1 Month to <2 Years (N=20)		2 to <5 Years (N=20)		5 to <18 Years (N=32)			
	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.

Assessor's comments

Most of the protocol deviations were related to the administration of the investigational product and concerned 'lab not done'. Four subjects had received >48 hrs of antifungal therapy at baseline and a total of four subjects had received >1 day of systemic antifungal therapy either during treatment or follow up.

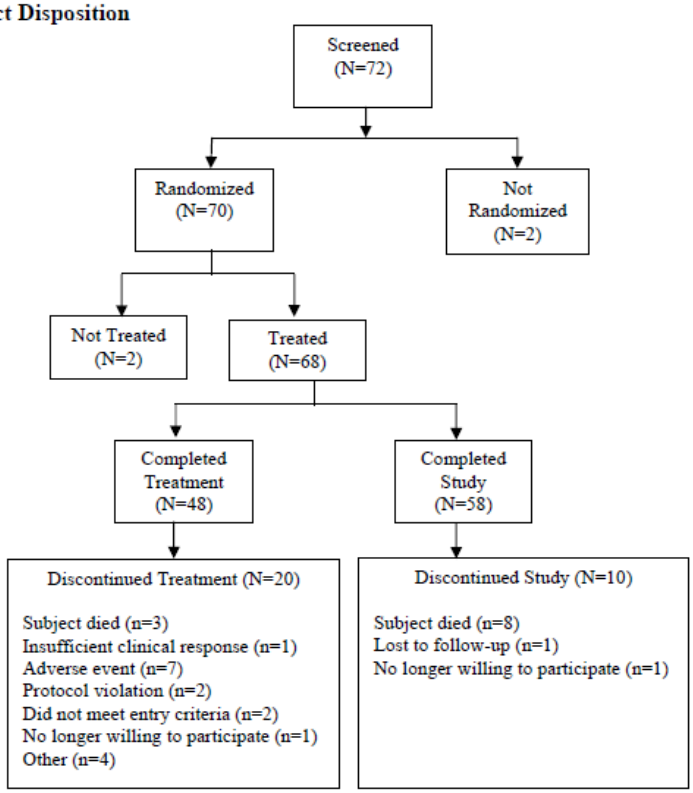
When submitting the type II variation application, the MAH should discuss the use of concomitant antifungal treatment and discuss the reasons (if not lack of efficacy), and whether these subjects were considered failures or not (according to protocol of a subject took 2 or more days of antifungal medications this persons was imputed a failure).

Recruitment / Number analysed

The study initiated in 2009 and completed its last subject last visit in 2018.

Over the 9-year study duration, 70 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.

Figure 2. Subject Disposition



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.

Of the 72 screened subjects, 4 subjects did not receive study drug and were not included in the safety population: 2 subjects were screen failures and 2 subjects 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 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 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
	1 Month to <2 Years (N=20) n (%)	2 to <5 Years (N=20) n (%)	5 to <18 Years (N=32) n (%)	(N=72) 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.

Assessor's comments

Within the 9 year period this trial ran for, 72 subjects were screened, 70 were randomised 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%) suggesting a high rate of protocol deviations which is not surprising considering the patient population.

Baseline data

Demographic characteristics are summarised 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*.

Assessor's comments

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 were 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*.

Efficacy results

Efficacy was evaluated as a secondary objective with relevant secondary outcomes being Global Response at EOIVT and subsequent timepoints, 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

		Age Group			Overall (N=64) n (%)
Time Point	Global Response	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)

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

Time Point	Global Response	Age Group: 1 Month to <2 Years (N=16) n (%)	Age Group: 2 to <5 Years (N=18) n (%)	Age Group: 5 to <18 Years (N=30) n (%)	Overall (N=64) n (%)

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

Assessor's comments

The global response rate at the end of IV treatment in the overall study population is 70.3% for the MITT population. Response rates are slightly 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), at 6-week FU it was 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

Over 90% of subjects overall and in each age group had blood only infection. 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 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 MAH 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

Assessor's comments

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 therefore 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/mm^3) at baseline (n=11) compared to those with ANC >500 cells/mm^3.

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.

Assessor's comments

Numbers are low (n=11) therefore data should be cautiously interpreted. The success rate is lower than in patients without neutropenia at baseline. Failure rates are not dissimilar however again, numbers are low.

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.

Assessor's comments

Clinical Cure and Microbiological response in the MITT is roughly in line with the Global Response.

Safety results

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.

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.

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.

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, generalised 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 anaesthetic 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 summarised 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 summarised 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 (see below under SAEs) was reported as an SAE.

Assessor's comments

Increased levels of hepatic enzymes have been 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. Evidently it is a risk also observed in paediatric patients and here similar precautions will need to be taken. It is unclear whether the risk is similar to that in adults based upon the available data.

Serious adverse events

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

- A 17-year old Asian male with underlying history of acute lymphocytic leukaemia 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.
- A 5-year old 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 tumour progression on MRI. During enrolment, multiple AEs were reported, including, among others: bradycardia (Days 2 and 4), pyrexia (Day 2 to 10), tachypnoea and respiratory disorder (Day 3 to 4); scrotal oedema (Day 5 onward), penile oedema (Day 7 onward), and dyspnoea (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.
- A 3-month old 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 MAH; 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:

- A 7-year old Asian male, discontinued anidulafungin after 1 dose due to a treatment-related AE of pruritus generalised. 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 haemorrhage, 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.

- A 3-year old 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."
- A 17-year old Asian male, died of sepsis (on Day 18; causality was reported as being related to acute lymphocytic leukaemia). 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*.

2.3.4. Discussion on clinical aspects

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. Although the study would have benefitted from a control arm, in general the methods are considered appropriate.

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.

The pharmacokinetic behaviour of anidulafungin in children has only partially been characterised. Results of the awaited population pharmacokinetic modelling should be presented and assessed, before conclusions on the pharmacokinetics can be drawn.

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.

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 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%).

The overall global response success rates in the MITT population 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), at 6-week FU it was 56% (71/127).

As over 90% of subjects in the MITT population had *Candida* isolated from blood only, global response rates in subjects with candidaemia (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.

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 occuring less frequently than roughly 1 in 10 paediatric subjects. There were no clear age-related patterns in the safety data 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. It is unclear whether the risk is similar to that in adults based upon the available data, however evidently similar precautions will need to be taken in paediatric patients.

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.

3. Rapporteur's overall conclusion and recommendation

Overall the data provided by study A8851008 suggests that the efficacy and safety in paediatric patients aged 1 month to 18 years with invasive candidiasis/candidaemia is largely in line with the efficacy and safety profile seen in adults. However data are limited and pharmacokinetics are not yet fully characterised, therefore this assessment is only preliminary. The submission of a Type II variation application in 2019 to update the Product Information as supported by the A8851008 CSR and the final PMAR for the aforementioned population PK/PD analysis is awaited.

☒ Fulfilled:

In view of the available data regarding paediatric patients aged 1 month to 18 years with invasive candidiasis/candidaemia, the MAH should either submit a variation application in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided by end of February 2019.