SCIENTIFIC DISCUSSION

1. Introduction

Candida infections - epidemiology

The yeast *Candida* is the most common fungal pathogen and constitutes a significant medical problem. *Candida* species have emerged as one of the leading causes of nosocomial blood stream infections. The increasing use of broad-spectrum antibiotics, cytotoxic chemotherapy, stem cell/solid organ transplantation, and the implementation of prosthetic devices and use of indwelling intravascular catheters account for the greater prevalence of systemic fungal infections during the past two decades. Immunosuppressed populations, including those who are neutropenic, run a high risk of serious and life-threatening *Candida* infections. *C. albicans* is the predominant clinical pathogen, although during the past decade the proportion of infections caused by non-albicans *Candida* species has increased exponentially. The use of azoles, in particular for prophylaxis, has been hypothesized to be a significant factor contributing to this change. The shift in epidemiology of *Candida* infections has important clinical and therapeutic implications since many non-albicans *Candida* species have an inherent decreased susceptibility to currently available antifungal agents. In addition, due to the widespread use of azoles, particularly fluconazole, resistant strains have increasingly emerged.

About the product

Anidulafungin is a semi-synthetic lipopeptide of the echinocandin B class, synthesized from a fermentation product of *Aspergillus nidulans*. The chemical name for anidulafungin is 1-[(4R, 5R)-4, 5-dihydroxy-N(2)-[[4"-(pentyloxy)[1,1':4',1"-terphenyl]-4-yl]carbonyl]-L-ornithine]echinocandin B.

Echinocandins are inhibitors of fungal cell wall biosynthesis. Echinocandins exert their effect by disrupting the synthesis of 1,3-beta-D-glucan, an integral component of the fungal cell wall. Their mechanism of action differs from those of established classes of widely used systemic antifungal agents, which affect cell membrane sterols, either by direct interaction with them (polyenes, represented by amphotericin B) or through inhibition of sterol synthesis (e.g. azoles, including fluconazole, itraconazole and voriconazole), or interfere with nucleid acid metabolism (flucytosine). Echinocandins, including anidulafungin, are expected to show no cross-resistance to other antifungal agents.

Anidulafungin is claimed to be active *in vitro* against *Candida* spp. including *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis, C. tropicalis, C. dubliniensis, C. lusitaniae,* and *C. guilliermondii* and *Aspergillus* species including *A. fumigatus, A. flavus, A. niger,* and *A. terreus.*

A Marketing Authorisation Application (MAA) for anidulafungin (Eraxis) - for *the treatment of oesophageal candidiasis*- in Europe had been withdrawn by the applicant in 2005. There were major Objections and Concerns related especially to the substantiation of efficacy of anidulafungin in that indication. In contrast, the present application seeks Marketing Authorisation (MA) in a different indication namely treatment of invasive candidiasis.

The claimed indication of anidulafungin was: "Treatment of invasive candidiasis, including candidaemia, in adult patients (see section 5.1)".

The finally approved indication is:

> "Treatment of invasive candidiasis in adult non-neutropenic patients.
>
> ECALTA has been studied primarily in patients with candidaemia and only in a limited number of patients with deep tissue *Candida* infections or with abscess-forming disease (see section 4.4 and section 5.1)."

2. Quality aspects

Introduction

Ecalta is formulated as a single use powder and solvent for concentrate for solution for infusion containing 100 mg of anidulafungin as active substance. Following reconstitution with the solvent provided (i.e. 20% (w/w) ethanol anhydrous in water for injections) to yield to a 3.33 mg /ml solution, the product is administered by intravenous infusion after dilution into an intravenous bag (or bottle) containing either 9 mg/ml (0.9%) sodium chloride for infusion or 50 mg/ml (5%) glucose for infusion (final concentration 0.36 mg/ml).

The other ingredients include:

- powder: fructose, mannitol, polysorbate 80, tartaric acid, sodium hydroxide, hydrochloric acid,
- solvent: ethanol anhydrous and water for injections.

The powder and the solvent are presented in type I glass vials closed by an elastomeric stopper with and an aluminium flip-off cap.

Active Substance

Anidulafungin is a semi-synthetic cyclic lipopeptide of the echinocandin B class.
Anidulafungin is a white to off white solid, which is insoluble in water and it is slightly hygroscopic.
There are fifteen asymmetric centers in the Echinocandin B (ECB) nucleus of Anidulafungin. The active exhibits minimal crystalline properties. Polymorphism and particle size are not of relevance, considering the nature of the product i.e. lyophilised powder to be administered as a solution.

- Manufacture

Anidulafungin is obtained by a semi-synthetic process comprising fermentation steps followed by three synthetic steps. It is prepared from 2 starting materials, one being the Echinocandin B (ECB) nucleus of Anidulafungin obtained by fermentation.

The fermentation steps comply with the PhEur monograph on “Products of fermentation” where relevant. They have been satisfactorily validated as well as the critical synthetic steps. Satisfactory specification and associated methods have been provided for the starting materials, key intermediates, reagents and solvents used in the fermentation and synthetic steps as relevant. Process impurities originating from each starting material/reagent/solvent and during the process have been adequately discussed and limits defined in the active substance specification as appropriate.
Stereo-isomeric purity of anidulafungin is not a matter of concern as the configuration of the asymmetric centers is fixed by the producing microbiological organism, single crystal X-ray crystallography has shown that the atoms comprising the ring structure of Echinocandin B (ECB) nucleus are locked, processing conditions does not allow for optical inversion and ensure that there is not significant amount of cyclopeptide ring opening, and the control methods can measure ring opened product.

For stability purposes, D-fructose is added to the active. The mixture of D-fructose and Anidulafungin is non-stochiometric, the fructose is not tightly bonded and it is dissociated when dissolved.
The fructose content in the active substance has been satisfactorily justified based on stability data.

- Specification

The active substance specification includes tests controlled by validated methods for appearance, identity (IR and HPLC), assay (HPLC), fructose content, organic impurities (HPLC), residual solvents (GC), residue on ignition (PhEur), water content, heavy metals (PhEur), microbial limits (PhEur) and bacterial endotoxins (PhEur).

Impurity limits in the specification are justified by toxicology studies.

Batch analysis data provided for the fifteen batches manufactured at the commercial manufacturing site confirm satisfactory compliance and uniformity with the proposed specification.

- Stability

Data have been generated using anidulafungin stabilised with D-fructose.
Under long-term conditions (-20°C - commercial packaging), 3-year data have been provided for three batches manufactured at the commercial manufacturing/synthesis site. The shipping conditions proposed appear as acceptable.

The parameters tested included appearance, assay, impurities and water content.

The proposed retest period is supported by the presented data when stored in the proposed packaging.

Medicinal Product

Powder

- Pharmaceutical Development

The objective of the pharmaceutical development was to obtain a finished product that could be stored at room temperature.

Polysorbate 80 is used in order to improve solubility of anidulafungin, which is practically insoluble in water (see active substance). The target in-process pH (#4.3) selected is maintained by tartaric acid, which has been chosen because of its compatibility with the lyophilisation process. Fructose is included as a stabiliser based on good chemical stability data obtained for the active and for the finished product. Mannitol as a bulking agent facilitates lyophilisation.
Long term stability studies showed no incompatibility of anidulafungin with any of the excipents. All excipients are of PhEur quality and their specification include endotoxin and microbial contamination tests where relevant. Regarding the TSE risk, Ecalta does not contain any component of ruminant origin.

The 2.5% overfill has been shown to be appropriate to allow the label claim volume to be withdrawn from the vial after reconstitution.

The container closure system consisting of a type I glass vial closed by an elastomeric stopper with and an aluminium flip-off cap meet the PhEur requirements. With regards to the closure seal integrity, risk of sorption and leaking have been satisfactorily addressed. A compatibility study has been performed in order to review potential leachable compounds.

Compatibility of the finished product reconstituted with 20% (w/w) ethanol anhydrous in water for injections and further diluted into an intravenous polyvinylchloride bag containing either 9 mg/ml (0.9%) sodium chloride for infusion or 50 mg/ml (5%) glucose for infusion (final concentration 0.36 mg/ml) has been demonstrated (for in-use stability see stability of the product).

The formulation used in the pivotal phase III study was essentially similar to the intended product.

- Manufacture of the Product

The manufacturing process is a standard aseptic process including the following steps: compounding, sterile filtration, filling, lyophilisation and packaging.
Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture.

Validation data have been provided for three production-scale batches.

- Product Specification

The finished product specification includes tests for appearance, clarity of the reconstituted solution (PhEur), identification (IR, HPLC), pH, assay (HPLC), degradation products (HPLC), uniformity of dosage units (PhEur), water content (PhEur), bacterial endotoxins (PhEur), particulate contamination (PhEur), sterility (PhEur) and reconstitution time.
Batch analysis data provided for the three production-scale batches confirm satisfactory compliance and uniformity with the proposed specification.

- Stability of the Product

- Before reconstitution and dilution

Stability data are presented for 3 primary stability batches of the 100 mg vials and supportive data are presented for 50 mg vials batches.
For the 100 mg vials, up to 2-year data and 6 months data are available respectively under long term (25ºC/60%RH - proposed packaging - stored in inverted position) and under accelerated conditions (40°C/75% RH - proposed packaging - stored in inverted position). For the 50 mg vials 3-year data and 6 month data are available respectively under under long term (25ºC/60%RH - proposed packaging - stored in inverted position) and under accelerated conditions (40°C/75% RH - commercial packaging - stored in inverted position).
The parameters tested included appearance, assay, pH, water content, completeness and clarity of solution, reconstitution time, particulate matters degradation products, particulate contamination, reconstitution time and sterility.

- After reconstitution

Chemical and physical in-use stability of the solution reconstituted with 20% (w/w) ethanol anhydrous in water for injections has been demonstrated for 3 hours at 25ºC and for 2 hours at 5°C. The reconstitution time can be up to 5 minutes.

- After reconstitution and dilution

Chemical and physical in-use stability of the infusion solution has been demonstrated for 24 hours at 25ºC.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

The results presented support the proposed shelf life and storage conditions defined in the SPC for the finished product before reconstitution and dilution, after dilution and after dilution and reconstitution.

Solvent

- Pharmaceutical Development

20% (w/w) ethanol anhydrous in water for injections has been selected as reconstitution solvent over water for injections based on its ability to rapidly reconstitute the finished product in addition to significantly reduce foaming.
This introduces 6 g of ethanol into the concentrate after reconstitution (see section 4.4 of the SPC and section 2 of the package leaflet).
All the constituents are of PhEur quality and the solvent does not contain any component of ruminant origin. The packaging materials meet the PhEur requirements.
With regards to the closure seal integrity, risk of sorption and leaking has been satisfactorily addressed.

The 4.5% overfill has been shown to be appropriate to allow the label claim volume to be withdrawn from the vial.

- Manufacture of the Product

The manufacturing process is a standard process including the following steps: preparation of the bulk solution, filtration, filling into the vials, stoppering and sterilisation by autoclaving (22 minutes 121ºC). The sterilisation process is a standard PhEur method.
Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture.

- Product Specification

The solvent specification in include tests for appearance, clarity (PhEur), identity ethanol (GC), assay ethanol (GC), bacterial endotoxins (PhEur), particulate contamination (PhEur) and sterility (PhEur).
Batch analysis data provided confirm satisfactory compliance and uniformity with the proposed specification.

- Stability of the Product

Stability data are presented for 3 primary stability batches of the 30 ml vials and supportive data are presented for 15 ml vials.
For the 30 ml vials, up to 1-year data are available under long term (25ºC/60%RH - proposed packaging).
For the 15 ml vials 3-year data and 6 month data are available respectively under under long term (25ºC/60%RH - proposed packaging) and under accelerated conditions (40°C/75% RH - proposed).
The parameters tested included appearance, assay, particulate contamination and sterility.

Discussion on chemical, pharmaceutical and biological aspects

The active substance is well characterized and documented. The pharmaceutical form selected is adequate taking into account the properties and the stability of the drug substance. The excipients are commonly used for this kind of formulation and the packaging material is well documented. The manufacturing process enhances to obtain reproducible finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life. At the time of the CHMP opinion, there were minor unresolved quality issues having no impact on the benefit-risk- balance of the product. The applicant committed to resolve it as follow up measures after the opinion, within an agreed timeframe.

3. Non-clinical aspects

Introduction

The pivotal non-clinical safety studies were conducted under GLP conditions.

Pharmacology

- Primary pharmacodynamics

Anidulafungin is a non-competitive inhibitor of (1,3)-β-D-glucan synthase, an enzyme required for synthesis of β-linked glucan, which is a cell wall component of fungi. *In vitro* activity was demonstrated against *Candida* spp., *Aspergillus* spp., and *Pneumocystis carinii*. For *Candida* spp. except *C.parapsilosis*, MIC_{90} values were below the human therapeutic concentration of 7.2 mg/l. The *in vitro* activity of anidulafungin against *C.albicans*, *C.Glabrata*, *C.krusei* and *C.tropicalis* was at least equivalent to that of caspofungin, micafungin, fluconazole, itraconazole, voriconazole, posaconazole, amphotericin B, and flucytosine. Anidulafungin was also active against fluconazole-resistant isolates.

Activity of anidulafungin against *C.parapsilosis* was less than for most other antifungal agents. *In vitro* activity against *Aspergillus* species *fumigatus*, *terreus*, *niger*, *nidulans* and *flavus* was at least equivalent to that of itraconazole and amphotericin B. Resistance to anidulafungin has not been described to date. For other members of the echinocandin group, resistance has been reported rarely. Based on current data, fast emergence of resistance to anidulafungin is not very likely.

In vivo activity was demonstrated against *C.albicans*, *C.krusei*, *C.glabrata*, *A.fumigatus*, and *P.carinii*, based on survival studies and organ recovery studies, mainly performed in mice and rabbits. In some of the studies in mice, *Candida* was completely eradicated from the investigated organs (kidney and liver) at similar dosages (exposure based on AUC comparable to human therapeutic exposure) and treatment durations (3 days). In rabbits, exposures at or below the human therapeutic exposure for 7 – 10 days produced complete eradication of *C.albicans* from target organs stomach, duodenum, oesophagus, and spleen.

- Safety pharmacology programme

In smooth and cardiac muscle tissue of rats and guinea pigs, no effects were observed on non-stimulated muscarinic, β-adrenergic, α-adrenergic and angiotensin receptor activity. A slight (13%) but significant increase was observed in the force of angiotensin-induced contractions in guinea pig ileum. A significant decrease (45%) was observed in the EC_{50} of isoproterenol in isoproterenol-induced contractions in guinea pig trachea. The maximum tested concentration of anidulafungin (1.14 mg/l, free fraction) was at least 16-fold above the human therapeutic plasma concentration of 7.2 mg/l. No effect was observed on body temperature, grip strength, convulsive liability, hexobarbital-induced sleep time, auditory startle, and spontaneous activity in mice at dosages up to 20 mg/kg (exposure about 2-fold higher than the human therapeutic exposure based on AUC, see the table on interspecies). Lethargy was observed in rats at 20 mg/kg. No effects were observed on action potential duration in isolated rabbit Purkinje fibres. In an *in vivo* study in rats, anidulafungin did not cause arrhythmias. However, since in this study the ECGs were evaluated subjectively, QT intervals were probably not measured. A decrease was observed in systolic and diastolic blood pressure in rats, during the first hour after dosing. Also observed in rats, and possibly connected with the decreased blood pressure, are an increased heart rate, a decreased total urinary excretion of sodium (79%), a decreased fraction of filtered sodium in the final urine, and a decreased urinary volume (68%). In a study in telemetered monkeys, standard cardiovascular parameters were measured, also QT and RR intervals; no clinically relevant cardiovascular effects were observed.

- Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies have been performed *in vitro* with isolates of Candida and Aspergillus spp. This is further discussed in the clinical section of the report.

Pharmacokinetics

Animal PK studies were conducted in mice, rats, rabbits, dogs and monkeys using validated methods of analysis.

Most species tested (including humans) had similar anidulafungin pharmacokinetics across all studied doses. Anidulafungin volume of distribution, plasma clearance (CL), and $t_{1/2}$ were dose-independent in animal species. The drug is widely distributed in all species with volume of distribution approximately equivalent to the total body fluid content. Anidulafungin accumulates in the liver, spleen, lung and kidney. Plasma protein binding is high (>99%) for rat, dog, monkey and human. Anidulafungin is not metabolised and, at clinically relevant concentrations, is not a substrate, inhibitor, or inducer of the hepatic cytochrome P450 (CYP) system. Anidulafungin chemically degrades slowly to a ring-opened product that is further degraded. Faecal elimination is the major route of elimination for anidulafungin and its degradation products. A fraction of the administered dose is eliminated as intact anidulafungin by both biliary and non-biliary mechanisms.

Toxicology

- Single dose toxicity

Acute IV toxicity in rats indicated an LD50 of 71 mg/kg. Mice survived after a single dose of 100 mg/kg. Overt symptoms consistent with an infusion reaction (e.g. swollen snout, red ears, hypoactivity) and haemoglobinuria occurred at 50 mg/kg in both species. In rats, there were several overt symptoms, which were suggestive of oedema and a disturbed water balance (excessive drinking, swollen muzzles, moist pancreas).

- Repeat dose toxicity (with toxicokinetics)

Repeated-dose studies were performed in 1 month- and 13 week studies in rats and monkeys. In rats, the principal overt symptom was a dose-related (10 mg/kg/day and higher), but transient, infusion reaction. Signs (e.g. swollen snout, red ears, hypoactivity) generally dissipated after a few days of dosing. The 1 month- and 13 week repeated-dose toxicity studies showed that treatment with anidulafungin leads to an increase in absolute/relative weight of spleen and lung and liver in the rat. In this species, the observed hepatic effects included microscopic cellular changes (polykaryocytosis, karyomegaly, hypertrophy sinusoidal lining cells, vacuolation) and necrosis, leading to the release of liver enzymes into the circulation (ALP, AST, ALT, GGT). In the monkey, only an increase in absolute/relative weight of the liver was observed. In this species, a high dose of 30 mg/kg/day for 1 month resulted in mildly to moderately increased cholesterol concentrations and ALP activity. Transient, mild to moderate increases in serum enzymes indicative of liver injury (ALT and AST) were also noted in a few animals. A dosage of 35 mg/kg/day administered for 13 weeks to monkeys was associated with moderately higher cholesterol concentration and mildly higher ALP activity, increased absolute and relative liver weights (approximately 40%) in males, and minimal multifocal hypertrophy of sinusoidal and peri-sinusoidal cells which contained blue-staining material. Animals, allowed to recover for 1 month after the cessation of dosing, no longer exhibited elevated ALP or cholesterol, but microscopic liver changes were observed in 2 of the 4 animals that had received 35 mg/kg/day.

High (at least 30 mg/kg/day) IV doses in rats were also associated with moderate effects on body weight gain, skeletal myopathy, effects on the thymus, epididymis, and kidneys, and histological changes in several tissues suggestive of an effect on the reticuloendothelial system (RES) involving an increase in the number of secondary lysosomes. In the 1 month and 13 week studies, the plasma cholesterol was increased at dosages of 6.6 mg/kg/day and higher. A mild, regenerative anaemia, haemoglobinuria and red discharge in the eyes were also seen. The cause of these effects is unknown but is probably due to haemolysis. These effects were not seen in monkeys. Partial-to-complete recovery of all clinical pathology parameters plus, in some cases, reduced severity of microscopic findings, including liver changes, were noted 1 month after the end of dosing. The NOAEL for rats was 5 mg/kg/day and for monkeys was 10 mg/kg/day for 13 weeks days of daily dosing.

- Genotoxicity

Anidulafungin was non-genotoxic in several Bacterial Reverse Mutation Assays (Ames tests) and in Chromosomal Aberration Tests *in-vitro* (CHO cells, mouse lymphoma cells) and *in vivo* (mouse micronucleus test).

Various lots of anidulafungin were tested on genotoxic potential and in two repeated dose studies. Different toxicity profiles were observed in some lots. The positive results of two lots in the Ames test were caused by microbial contamination.

- Carcinogenicity

Long-term carcinogenicity studies with IV drug were not conducted.

- Reproduction Toxicity

No selective reproductive or developmental toxicity occurred in rats or rabbits when anidulafungin was administered. A combined reproductive, fertility and developmental toxicity (Segment I and II) study in rats only showed adverse reproductive and developmental effects at the highest dosage tested (20 mg/kg/day; NOAEL is 5 mg/kg). A rat peri- and postnatal toxicity (Segment III) study demonstrated maternal effects (infusion reactions at dosages ≥ 6 mg/kg/day) and decreased weight gain/food consumption (20 mg/kg/day); therefore, the maternal No Observable Effects Level (NOEL) was 2 mg/kg/day. A rabbit developmental toxicity (Segment II) study revealed maternal and developmental NOAELs of 10 mg/kg/day based on decreased maternal weight gain and 1 abortion, (probably secondary to decreased weight gain/food intake) and decreased foetal weight and metacarpal ossification observed with maternal dosages of 20 mg/kg/day.

- Local tolerance

An acute IV and perivascular irritation study was performed in rabbits. No adverse effects were observed. Anidulafungin has to be considered an ocular irritant for the rabbit eye, and was slightly irritant for the rabbit skin. Anidulafungin caused haemolysis in rat blood, but adverse effects were lacking in human blood. Anidulafungin had mild phototoxic potential in mouse fibroblasts, but no phototoxicity was observed in an *in vivo* photosafety study in rats at a single dose up to 30 mg/kg.

- Other toxicity studies

Anidulafungin did not adversely affect the humoral component of the immune system based on the results of a functional plaque assay performed with splenocytes. Bone marrow M:E ratios were not affected by any dose of anidulafungin. Nor did it decrease the cellular immune response as determined by anti-CD3-stimulated proliferation and lack of effects on the thymus. The increased spleen weight (dose-dependent), increased spleen cell number (not dose-dependent), and the increased antiCD3-stimulated proliferation (at the highest dose of 30 mg/kg/day) could indicate an increased T cell response. The spleen effects are probably due to the slight activation of the RES in rats. This activation was not observed in monkeys, so is not expected to be clinically relevant.

Ecotoxicity/environmental risk assessment

The applicant has provided an environmental risk assessment prepared in accordance with the current Note for Guidance. Since anidulafungin is a lipopeptide and subject to significant degradation, it may be concluded that anidulafungin will not present an environmental risk following patient use.

Discussion on the non-clinical aspects

In 3-month studies, evidence of liver toxicity, including elevated enzymes and morphologic alterations, was observed in both rats and monkeys at doses 4- to 6-fold higher than the anticipated clinical therapeutic exposure.

Long-term carcinogenicity studies with IV drug were not conducted. This was considered acceptable by the CHMP since anidulafungin was found to be non-genotoxic and to have no selective reproductive or developmental toxicity and because long-term clinical IV dosing is not anticipated. Furthermore, a retrospective study in archival liver samples of a 3-months rat study showed that anidulafungin given to rats intravenously at doses up to 30 mg/kg/day for 13 weeks did not produce increased numbers of hepatic foci of cellular alteration, hepatocellular regenerative hyperplasia, or hepatocellular neoplasia.

4. Clinical aspects

Introduction

In this assessment the focus is on new data not discussed in the assessment of the previous MAA. The PK data assessment from the previous MAA is updated for so far necessary in this AR together with an update on the PD data. The assessment of the previously provided data on the efficacy and safety of anidulafungin in the treatment of oesophageal candidiasis is integrated into the present assessment as supportive data for the safety of Anidulafungin (Eraxis).

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

During assessment it was noted that FDA submitted a request for an independent audit for the pharmacokinetic data for the studies VER-002-010 (a mass balance study of ^{14}C-anidulafungin), VER-002-012 (a study to examine the safety, tolerability, and pharmacokinetic profile of IV anidulafungin in immunocompromised children with neutropenia, ages 2 to 17 years) and VER-002-013 (an interaction study with voriconazole (Vfend)).

In the opinion of the CHMP, these 4 studies are supportive and have no impact on the evaluation of the benefit/risk ratio for Ecalta. The outcome of the audit will be dealt with via a Follow-Up Measure.

Pharmacokinetics

To support the application of anidulafungin, 5 single and multiple dose studies with an oral formulation were submitted and 13 studies with the intravenous formulation, including one study in children. In addition, 4 studies were included in population pharmacokinetic analysis.

A total of 124 subjects (healthy subjects, subjects with HIV, or with fungal infections) received the oral study drug and were included in the pharmacokinetic analysis. For the intravenous formulation, pharmacokinetic data were obtained from 226 subjects without fungal infections (including subjects with HIV, hepatic impairment, and renal impairment) and from about 262 subjects with fungal infections. Pharmacokinetic data were also obtained from 24 immunocompromised children with neutropenia.

- Absorption

After oral administration of anidulafungin it appeared that the absolute bioavailability was low (2 – 7%) and the variability in the pharmacokinetic variables high (ca. 50%). Therefore the i.v.formulation was chosen for further development and thus the absolute bioavailability of this formulation is not considered to be an issue (100%).

Anidulafungin showed linear pharmacokinetics after once daily dosing over the dose range of 15 – 130 mg. Using a loading dose of twice the daily dose, steady state was received at the second dose. No unexpected accumulation occurs. At a loading dose of 200 mg and a daily dose of 100 mg, C_{max} was about 7.2 µg/ml, AUC_{ss} ca. 110 µg.h/ml and C_{min} about 3.3 µg/ml. The recommended infusion rate of ca. 1 mg/min (0.5 mg/ml solution) was based on adverse events which were observed at higher infusion rates.

- Distribution

In vitro protein binding studies using human plasma indicate that protein binding is about 99%. The volume of distribution (0.6 l/kg) is comparable to total body fluid. Anidulafungin does not accumulate

in erythrocytes. Animal data indicate that anidulafungin accumulates in liver, spleen kidney and lung, and crosses the placenta and is excreted into mother milk.

After administration of radio-labelled anidulafungin, a long elimination half-life of plasma radioactivity (about 268 hours) was observed. This half-life was estimated by using only 2 time points and considered not reliable. Although the low incidence of observed hepatic AEs in ICC patients suggest no covalently bind to albumin, this cannot be ruled out. Nevertheless, although the risk appears low, the proposed SPC warns for the potential for hepatic effects when treating patients with anidulafungin. In addition, a Pharmacovigilance follow-up measure with regard to hepatic safety and elucidation of the covalent binding was requested.

- Elimination

In vitro and in vivo data indicate that anidulafungin undergoes transformation in a ring-opened product as a result of non-enzymatic degradation. The ring-opened product, a linear peptide, is considered to be a substrate for further metabolism by non-specific peptidases (into small peptides). About 40% of the drug-derived radioactivity exposure in plasma was due to anidulafungin, and the remaining 60% of the exposure in plasma was due to biotransformation products. About 29 ± 13% of the administered radioactive dose was recovered in faeces over 9 days, of which less than 10% of the dose as intact drug. Only 0.56 ± 0.12% of the administered radioactive dose was recovered in urine.

The ring-opened product and the other biotransformation products (small peptides) are considered to have no pharmacological activity, as they lack the cyclo-peptide ring structure which is required for antifungal activity.

The elimination half-life of anidulafungin is about 40-50 hours, and total body clearance about 16 ml/min which was independent of dose and not affected by repeat administration.

- Special populations

With regard to patients with an impaired renal function, patients with an impaired liver function, elderly, age and race, the pharmacokinetics are not significant altered. The SPC gives no special dose recommendation. This is agreed based on the pharmacokinetics.

In a population pharmacokinetic analysis, a small increase (ca. 20%) in clearance was observed in male subjects compared with female subjects. The weight effect was within about 30% comparing the extremes of the weight borders (40 and 150 kg) with the normal weight group (70 kg).

Comparable steady state concentration-time profiles were obtained in children receiving 0.75 and 1.5 mg/kg/day anidulafungin and adult patients receiving 50 and 100 mg/day anidulafungin, respectively.

- Pharmacokinetic interaction studies

As observed from the in vitro and in vivo metabolism studies, anidulafungin is expected to have a low interaction profile. This was also indicated by the pharmacokinetic population analysis, showing no significant influence of CYP450 inducers, inhibitors, and rifampicin. In vivo, a small but significant decrease (ca.16%) in the anidulafungin plasma clearance was observed when co-administered with cyclosporin A, which is considered not clinically relevant. In vivo, no interaction is observed with voriconazole, tacrolimus and amphotericin B.

Pharmacodynamics

- Mechanism of action

Anidulafungin, like other echinocandins, is a non-competitive inhibitor of 1,3-beta-D-glucan synthase, an enzyme required for the synthesis of beta-linked glucan polymers, which comprise a major structural component of the cell wall of many pathogenic fungi. As interference with cell wall glucan production results in osmotically fragile cells that are easily lysed, anidulafungin has fungicidal activity.

- Primary and Secondary pharmacology

Breakpoints are currently not available for anidulafungin. MICs were determined according to the Clinical and Laboratory Standards Institute (CLSI) approved standard reference method M27 for yeasts.

Studies in vitro

Anidulafungin shows activity in vitro against a number of important pathogenic organisms, including *Candida* spp., *Aspergillus* spp., and *Pneumocystis carinii*. Against *Candida* and *Aspergillus*, anidulafungin is at least as potent as, and often more potent than, amphotericin B and fluconazole.

Activity against *Candida* species in vitro has been assessed in at least 23 studies, which included more than 11 000 isolates of at least 14 species (including polyene- and azole-resistant isolates) from more than 390 centres worldwide. Most of these isolates were obtained from the bloodstream, whilst many others (mainly obtained from HIV-infected patients) came from oropharyngeal mucosa. For most *Candida* species, anidulafungin MIC_{90}s were comparable to or lower than the MIC_{90}s of established antifungal agents. Where fungicidal activity was assessed, anidulafungin showed concentration-dependent activity against *Candida* species.

In vitro studies demonstrated no antagonism when anidulafungin was combined with fluconazole, amphotericin B, itraconazole or flucytosine against *Candida* species, nor with amphotericin B against *Aspergillus* species.

Studies in animal models

In animal models, anidulafungin has cleared *Candida* from internal organs and mucosa and prolonged survival in lethal infections. Efficacy of anidulafungin against *A. fumigatus* infections in mouse and rabbit models, and against *P. jiroveci* in mice and rats has also been described.

Clinical trials

Overall, the epidemiology of the baseline pathogens across the three Phase 2 and Phase 3 studies in invasive candidiasis was similar to other studies of candidaemia, with the most common pathogens being *C. albicans* followed by *C. glabrata, C. parapsilosis* and *C. tropicalis*. The lower proportion of non-*albicans* species, in particular *C. glabrata* in the pivotal study VER002-9 (approx. 20% vs. approx. 2-fold higher in the other studies) is explained by the exclusion by investigators of patients infected with this organism in the pivotal study VER002-9, which used fluconazole as the comparator-since *C. glabrata* is often resistant to fluconazole.

With the 200/100 mg loading/maintenance dose regimen used in the ICC studies, the peak plasma concentration exceeds 6 mg/l, and concentrations greater than 2 mg/l are maintained throughout therapy. These are well above the MIC_{90}s that were determined in vitro for *Candida* species. Anidulafungin MICs above 0.06 mg/l were infrequent, however. Overall, there was no clear relationship between echinocandin activity in vitro and actual patient response. See display in the following table.

Table 1 Successful By-Pathogen Microbiological Responses by Anidulafungin MIC

MIC (mg/l)	Successful Response* [n/N (%)]
≤ 0.002	48/50 (96)
0.004	23/26 (89)
0.008	22/22 (100)
0.015	11/15 (73)
0.03	11/13 (85)
0.06	8/9 (89)
0.12	1/3 (33)
0.25	2/2 (100)
0.5	6/7 (86)
1	4/6 (67)
2	2/3 (67)
Unknown	11/13 (85)

* Patients Treated with 100 mg Anidulafungin Daily in studies VER002-9 and VER002-9B Combined- -ITT, End of IV Therapy

In the invasive candidiasis studies, 73% of baseline pathogens were from the US, and 96% from the US and Canada combined. Nevertheless, the overall species distribution was similar for most countries, and MIC ranges and distributions were also similar in different geographical areas. When similar test conditions were used, anidulafungin MICs were similar within species for isolates from different geographic areas, different studies, and different anatomical sites of infection.

Resistance

To date, there has been no documented report of resistance to anidulafungin in clinical study isolates or non-clinical study isolates of *Candida* species.

Recent limited data on clinical isolates suggest incomplete cross-resistance among the few reported micafungin or caspofungin resistant *Candida* isolates that have been tested.

PK/PD

PD and PK/PD studies in healthy subjects were not conducted.

A population pharmacokinetic/pharmacodynamic (PK/PD) analysis was performed to evaluate the association between exposure and efficacy and safety endpoints based on individual data from four studies (VER002-4, VER002-6, VER002-7 and VER002-11). Minimum inhibitory concentration (MIC) testing was performed in three studies (VER002-4, VER002-6 and VER002-11). The MIC-0 (defined as 95%-100% growth inhibition after 24- h incubation) values at the baseline were used for PK-PD index evaluation such as AUC/MIC, where AUC is the area under curve.

Study VER002-6 was the only Phase II trial in invasive candidiasis included in this PK/PD analysis. The other studies are not immediately relevant for the present indication because of the other indications (in patients with different disease and demographic characteristics) and lower doses tested and the questionable design of some of them:

> VER002-4 is the pivotal comparative study in oesophageal candidiasis which tested a lower dose – 2 fold lower than presently sought.
>
> VER002-7 was a Phase II, open label, non-comparative study of the safety and efficacy of IV anidulafungin plus AmBisome [(amphotericin B) as a treatment for invasive aspergillosis (IA). Patients received anidulafungin treatment (200/100 mg) in combination with AmBisome (dose up to 5 mg/kg/day) up to 90 days. The combined treatment design (non-factorial) with anidulafungin (single dose level) plus amphotericin B in a different indication does not help to elucidate the contribution of anidulafungin exposure to safety and efficacy in the presently sought target population.

VER002-11 was a Phase II, open label study of the safety and efficacy of IV anidulafungin 100/50 mg as a treatment of (19) patients with azole-refractory mucosal candidiasis; again the indication and single dose lower level of anidulafungin not helpful in deriving relevant PK/PD data for the present indication.

Focusing on study VER002-6, the probabilities of success at global response at the end of therapy and at the 2-week follow-up were positively associated with AUC (n = 87), but not with AUC/MIC (n = 71). Adequate characterization of the effect of anidulafungin exposure on response could not be established in all treated patients due to the small sample size. No trend was observed in the clinically evaluable patients.

As noted earlier, in the population pharmacokinetic analysis, the weight effect was within about 30% comparing the extremes of the weight borders (40 and 150 kg) with the normal weight group (70 kg). Additional analyses indicate that high body weight did not seem to impact adversely on efficacy, whereas the number of patients on the low end of the weight spectrum (n=12) is too small to allow any indicative conclusions (suggesting an excess number of adverse events due to high exposure). The applicant committed to collect data for patients on the low end of the weight spectrum as part of the ongoing PSURs.

Clinical efficacy

The clinical evidence of efficacy and safety of anidulafungin in the newly sought indication is based on the results of a pivotal randomised double-blind comparative study. In addition supportive non-comparative data provide further support for efficacy/safety. See the table below.

Table 2 Phase II/III Intravenous Anidulafungin Studies in ICC

Study	Design	Anidulafungin Maintenance Dose (mg/day, IV)*	Location	ITT population
VER002-9	DB, comparative vs. Fluconazole	100	USA, Canada, IT, DE, NL	131 anidulafungin 125 fluconazole‡
VER002-9B	Open label	100	USA, Canada	33
VER002-6	Open label	50, 75, 100	USA	120
XBAG †	DB, vs. fluconazole	25, 35	USA, BE, South Africa	3 anidulafungin 2 fluconazole‡

* Day 1 loading dose was twice the maintenance dose in all phase 2/3 studies.
† Raw data not available for Study XBAG.
‡ In Studies VER002-9 and XBAG, fluconazole was administered as a 800 mg IV loading dose and thereafter at 400 mg IV daily, with dose adjustments for renal insufficiency.

XBAG, was conducted by the original sponsor but was discontinued after only 5 patients were enrolled. The current applicant does not have access to the raw data for this study.

For the other 3 "invasive candidiasis" (ICC) studies, study drug was to be administered for a minimum of 14 days following the last negative culture or commencement of improved signs and symptoms (whichever occurred later), for a maximum of 42 days.

In all 3 studies, median age was between 51.5 and 59 years. Most patients (~90%) had candidaemia only and, with the exception of the 75mg dose in VER002-6, approx. 20% of patients in each study had an APACHE II score > 20, scores > 20 being indicative of a sick population often found in intensive care units. It should be noted however, that there was a percentage of patients in each of the VER002-6 study arms that had unknown APACHE scores. Diabetes mellitus and renal failure were common co-morbidities and the use of central venous catheters, broad-spectrum antibiotics, recent surgery and neoplasia were common risk factors among patients in studies VER002-9 and VER002-9B.

- Dose response studies

In the Phase II, dose ranging study VER002-6 loading/maintenance dose regimens of 100/50 mg, 150/75 mg and 200/100 mg were evaluated in patients with invasive candidiasis and candidaemia. Despite wide overlap of confidence intervals, there was a suggestion of dose-response the observed trend favouring the two higher doses of anidulafungin (150/75 mg and 200/100 mg). Further details of this study are provided under section "Supportive studies" (below).

Although the study was not powered to distinguish definitively between the 150/75 mg and 200/100 mg doses, both appeared well tolerated; it was therefore decided to advance the higher of the doses for study in the Phase III trial (Study VER-002-9) in order to achieve and maintain the highest possible plasma concentrations.

- Main study

Study VER002-9

This is a Phase 3, double-blind, randomised, non-inferiority study comparing anidulafungin and fluconazole in the treatment of patients with candidaemia and other forms of invasive candidiasis.

METHODS

Study Participants

One hundred and thirty-one (131) patients were enrolled and randomised to anidulafungin and 125 to fluconazole. The diagnosis was based on a blood culture or a culture from another normally sterile site. Osteomyelitis and endocarditis were excluded primarily because these conditions are liable to require especially long courses of treatment (the maximum duration of treatment allowed in this protocol was 42 days), whilst meningitis was excluded because the blood-brain permeability of anidulafungin has not been fully defined.

Other main exclusion criteria were:

- Patients who received greater than 48 hours of systemic antifungal therapy for the *Candida* infection for which they were enrolled (In amendment #6 the 48-hour restriction was changed to 72 hours).

- Patients who received prophylactic administration of fluconazole, itraconazole, or voriconazole for more than one week within 30 days prior to enrolment.

- Patients who had received and who were to continue to receive terfenadine or cisapride (because fluconazole is contraindicated in these cases).

- Known *Candida krusei* infection (see below for reason).

- Patients with a known hypersensitivity to echinocandin therapy or azole therapy.

Only a few patients were *neutropenic* (defined as an ANC ≤ 500 cells/mm^3) at baseline, 5 in the anidulafungin and 4 in the fluconazole group (Micro-ITT Population).

Treatments

Fluconazole was chosen as comparator in Study VER002-9 on both efficacy and safety considerations.

Either anidulafungin (100 mg daily preceded by an initial 200 mg dose on Day 1) or fluconazole (400 mg daily preceded by an initial 800 mg dose on Day 1, with adjustments made for renal insufficiency) was administered daily by IV infusion for minimum treatment duration of 14 days from

the time of the last negative culture and improvement of clinical signs and symptoms of candidemia or invasive candidiasis. Total treatment duration was not to exceed 42 days.

In order to facilitate maintenance of the blind, patients were excluded if they had known *C. krusei* infection, since this organism is known to be resistant to fluconazole, and were discontinued from study/study drug if cultures revealed this organism after enrolment. For other (non-*krusei*) baseline species that were fluconazole-resistant, the investigator was to make the decision whether to continue on study medication according to the clinical and microbiological criteria customary to that hospital. *C. glabrata* seems to have been often excluded because it is less susceptible to fluconazole.

Although the investigator was "encouraged" to continue IV therapy if at all possible, the protocol allowed for a patient from either treatment group to be switched to oral fluconazole for the remainder of treatment if the investigator felt it was appropriate to do so, if the patient had been afebrile for at least 24 hours and if the last blood culture was negative for *Candida* species.

Removal of central venous catheters, if possible, is generally recommended in the management of candidaemia. Consequently in the overwhelming majority of the patients the IV catheters were removed because the infections were attributed to the catheter by the investigator.

All *Candida* isolates were sent to a reference laboratory, where isolates were re-identified and tested to determine MICs of anidulafungin and other antifungal agents.

Objectives

Primary: To determine if anidulafungin is at least as effective as fluconazole with respect to the global response (clinical and microbiological outcome at the end of IV therapy) in the treatment of patients with a diagnosis of candidemia and/or other forms of invasive candidiasis.

Secondary: To compare anidulafungin to fluconazole in this patient population for safety, the prevention of late infections, and the clinical and microbiological efficacy at various time points.

Outcomes/endpoints

Definitions

***Intent-to-Treat (ITT) Population*:** All patients who received at least one dose of study medication were included in the ITT population.

***Microbiological Intent-to-Treat (Micro-ITT) Population*:** All patients who received at least one dose of study medication and who had a positive culture for *Candida* species from a normally sterile site preferably within 96 hours before entry into the study were included in the Micro-ITT population.

***Modified Micro-ITT Population*:** All patients who were in the Micro-ITT population and had a global response other than indeterminate at the end of IV therapy time point were included in the modified Micro-ITT population. This population was used in the analysis of the global response at the end of IV therapy time point only.

Primary efficacy endpoint

The primary efficacy endpoint was the successful Global (clinical and microbiological) response at the end of IV therapy (EOIVT). EOIVT was chosen as the test of cure (TOC) for the primary endpoint. The Micro-ITT population (microbiologic intent-to-treat) was the primary efficacy population. In the global response assessment, a patient was categorized as a *success* if there was both a clinical success and microbiological success. Clinical success however included cure and improvement in the definition: *cure* meant resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or oral fluconazole required to complete the course of therapy.

Improvement meant significant, but incomplete resolution of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment, or additional oral fluconazole required.

Microbiological success at the patient and pathogen level was defined as *eradication* (documented or presumed) whereby the culture was negative for all *Candida* species present at baseline (documented), or culture data were not available for a patient with a successful clinical response (presumed).

A patient was categorized as a *failure* if there was either a clinical or microbiological failure (excluded clinical and microbiological responses of indeterminate). A patient was categorized as *indeterminate* if there was a clinical and/or microbiological response of indeterminate and neither response was a failure.

Secondary efficacy endpoints

These included global response at all secondary time points in the Micro-ITT population and global response at all time points in the efficacy evaluable population; and clinical response at all time points in the Micro-ITT and efficacy evaluable populations.

The Efficacy Evaluable population was a subset of the Micro-ITT population. To be included in an efficacy evaluable population, a patient had no protocol violations affecting the time point for the population being considered.
Other secondary efficacy endpoints included, patient level microbiological response at all time points in the Micro-ITT and efficacy evaluable populations; and pathogen level microbiological response in the Micro-ITT and efficacy evaluable populations at the end of IV therapy and 2 week FU time points only.

Death directly attributable to invasive candidiasis/candidaemia and all cause mortality were also assessed.

At the end of oral therapy, clinical success was defined as complete resolution or significant improvement of signs and symptoms of the *Candida* infection; no additional systemic antifungal treatment required. At the follow-up (FU) visits success was defined similarly but it included success outcome at the end of IV therapy plus FU 2week visit success for the 6 week FU visit.

Sample size

If it was assumed that the two treatments were equally effective with global efficacy success rates of 70% at the end of IV therapy, 111 patients per treatment group were required to ensure with 90% probability (i.e., 90% power) that the lower bound of a 2-sided 95% confidence interval (CI) for the true difference in efficacy (anidulafungin minus fluconazole) was not less than -20%. The Micro-ITT population was the primary efficacy population. It was expected that less than 10% of patients would not have a *Candida* species and thus, not be included in the Micro-ITT population. Therefore, 248 patients were to be enrolled to obtain 222 Micro-ITT patients.

Assuming that 25% of the enrolled patients would not be efficacy evaluable at the end of IV therapy, there would be 186 patients, or 93 per treatment group, in the secondary analysis (evaluable) population. This would provide at least 80% power to ensure that the lower bound of a 2-sided 95% confidence interval (CI) for the true difference in efficacy (anidulafungin minus fluconazole) was not less than -20%.

Randomisation

Patients were stratified according to their APACHE II score ($\leq$20 and > 20) and absolute neutrophil count (ANC) ($\leq$500 and >500). The patients were then randomly assigned (1:1 ratio) to receive either IV anidulafungin or IV fluconazole according to a centralized, automated interactive voice response system (IVRS).

Blinding (masking)

All unit doses of study drug were prepared at the study sites by designated unblinded members of the clinical pharmacy staff or study staff. The person assigned this responsibility did not anticipate in the care or evaluation of the patient. The unblinded staff member was not permitted to administer the study medication to the patient. The study medication was given to the Investigator or to the Investigators (blinded) designee for administration to the study patient. The study coordinator and Investigator remained blinded to the study medication used by any individual patient. The total volume for infusion and infusion rate were identical for both study arms.

Statistical methods

The protocol specified that anidulafungin would be considered non-inferior to fluconazole if the lower bound of the 95% CI (calculated around the difference between the global response rates of the 2 treatment groups) exceeded -20%. A 2-step analysis was specified: should non-inferiority be demonstrated at the primary endpoint, a further test for superiority (lower bound of 95% CI > 0) would also be performed. The applicant states that the chosen wide delta of -20% has been influenced by previously reported studies in echinocandins, though in retrospect a narrower value might have been preferable.

RESULTS

Participant flow

Two hundred sixty-one (261) patients were randomised to treatment, 256 patients received at least one dose of study medication, and 174 (174/256, 68.0%) completed the study through the 6-week follow-up.

A summary of patient disposition is presented in the following table:

Table 3 Patient disposition and reasons for withdrawal

Category Event	Anidulafungin n (%)	Fluconazole n (%)
Total randomized	132	129
Intent-to-Treat	131	125
Total completed the study through 6 week follow-up	94 (71.8)	80 (64.0)
Total discontinued from study prior to 6 week follow-up	37 (28.2)	45 (36.0)
Death	29 (22.1)a	38 (30.4)b
Patient lost to follow-up	8 (6.1)	7 (5.6)
Total completed full course of study medication[c]	97 (74.0)	77 (61.6)
Total withdrawn from study medication[d]	34 (26.0)	48 (38.4)
Adverse Event	12 (9.2)	21 (16.8)
Patient Withdrew Consent	5 (3.8)	4 (3.2)
Patient Noncompliant	1 (0.8)	0
Worsening Clinical Status/Lack of Efficacy	11 (8.4)	16 (12.8)
Investigator Discretion	5 (3.8)	5 (4.0)
Vicuron's Request	0	1 (0.8)e
Patient Lost To Follow-Up	0	1 (0.8)

NOTE: Percentages are based on the ITT population.
a: Patient 27-003 died after the 6-week follow-up period and is not included in this table.
b: Patient 40-014 was counted as completing the study through the 6-week follow-up period on the CRF termination page with a completion date of 11 Aug 2004, although the patient died on the same day and was counted in the number of deaths in the time to death.
c: .Total completed full course of study medication refers to completion of IV and oral (if applicable) study medication.
d: For each patient who withdrew from study medication, only 1 reason (the primary) for withdrawal is tabulated.
e: Patient 07-008 had study medication discontinued by Sponsor request due to a diagnosis of cryptococcal meningitis.

Of the patients who received at least one dose of study medication 131 patients were randomised to anidulafungin and 125 to fluconazole (ITT population). The rate of withdrawal from the study was higher in the fluconazole arm mainly due to death before the 6-week follow-up visit or due to adverse event (AE) or for lack of efficacy.

Twenty-eight (28) patients in the anidulafungin arm and 34 patients in the fluconazole arm had protocol violations that led to exclusion from the efficacy evaluable population at end of IV therapy. Overall, the most common protocol violations were indeterminate clinical response at 6-week follow-up visit and indeterminate clinical response at 2-week follow-up visit for patients in both study arms.

Baseline data

The two treatment groups were well balanced with respect to baseline and demographic characteristics. However, there were numerically more patients in the fluconazole group who had a risk factor of immunosuppressive therapy (22.9% vs. 14.2% for anidulafungin) listed at baseline.

In both treatment groups fluconazole was the most frequently used prior antifungal agent, 62.6% of patients in the anidulafungin group vs. and 68.8% in the control arm. This was followed by caspofungin/amphotericin B (in 4- 6%/ approximately 5% of the patients respectively per arm). The majority of patients who received prior fluconazole took it within 48 hours of study start, presumably for empiric therapy for invasive candidiasis. Nine (9) patients (7 in the anidulafungin arm and 2 in the fluconazole arm) had prophylactic low dose fluconazole therapy of less than 7 days duration before the first dose of study medication. In a few cases (3 anidulafungin-treated patients and 2 fluconazole treated patients), the prior fluconazole use (of $\geq$3 days) was the protocol violation that made the patients not efficacy evaluable at end of IV. A few patients in both treatment arms received non-protocol-specified antifungal medication while taking study medication.

For both arms, approximately half of all patients had invasive candidiasis related to an IV catheter by investigator assessment. Most (95.2% anidulafungin; 85.9% fluconazole) of these patients had the catheter removed as part of the medical management for invasive candidiasis/candidemia.

Numbers analysed

Greater than 90% of patients had a baseline *Candida* species and were included in the Micro-ITT population. The Micro-ITT population was comprised of 245 patients; 127 (127/131, 96.9%) in the anidulafungin arm and 118 (118/125, 94.4%) in the fluconazole arm. The Efficacy Evaluable population at the end of IV therapy was a subset of the Micro-ITT population. The percentage of patients evaluable for efficacy was 78.6% for the anidulafungin arm compared with 72.8% for the fluconazole arm.

Outcomes and estimation

Most patients were not switched to oral fluconazole, but completed treatment with IV therapy in 74.0% 71.2% in the anidulafungin and fluconazole arm respectively. Overall median exposure to study drug (IV plus oral) was 15 days for the anidulafungin group and 14 days for the fluconazole group.

In the primary efficacy analysis, anidulafungin was statistically superior to fluconazole in the global response at the end of IV therapy in the Micro-ITT population, the global success rates were 96/127 (75.6%) and 71/118 (60.2%) respectively. The between group difference (anidulafungin minus fluconazole) in global success rate was 15.42% (95% CI: 3.85, 26.99).

Table 4 Global Success Rates in ICC in study VER002-9

		Anidulafungin n/N (%)	Fluconazole n/N (%)	Trt Diff (%)† (95% CI)
End of IV therapy	**Micro-ITT Population‡**	96 /127 (75.6%)	71/118 (60.2%)	15.42 (3.85, 26.99)
	Evaluable Population	90/103 (87.4%)	68 /91 (74.7%)	12.65 (1.66, 23.65)
End of oral therapy	**Micro-ITT Population**	31/33 (93.9%)	28/33 (84.8%)	9.09 (-5.60, 23.79)
	Evaluable Population	28/30 (93.3%)	26/27 (96.3%)	-2.96 (-14.38, 8.46)
End of all therapy	**Micro-ITT Population**	94/127 (74.0%)	67/118 (56.8%)	17.24 (5.49, 28.99)
	Evaluable Population	88/103 (85.4%)	64/87 (73.6%)	11.87 (0.37, 23.37)

‡ Primary endpoint
† Treatment difference for anidulafungin minus fluconazole.

In a post-hoc analysis, comparison of the two arms in patients receiving immunosuppressive therapy (in the Micro-ITT population) as a risk factor for invasive candidiasis revealed that 12/18 (66%) anidulafungin-treated patients had global success at the end of IV therapy, compared to 16/27 (59.3%) of fluconazole-treated patients.

In all secondary efficacy analyses, success for the anidulafungin arm was greater than fluconazole (end of all therapy and 2-week follow-up time points), or at least as effective as fluconazole (end of oral therapy and 6-week follow-up time points), consistent with the primary efficacy analysis. Results in the efficacy evaluable populations were similar.

In a modified Micro-ITT analysis of the primary efficacy population (minus patients whose global response was indeterminate) the global response at the end of IV therapy anidulafungin was superior to fluconazole with success rate of 96/109 (88.1%) vs. 71/95 (74.7%) for fluconazole (95% CI: 2.69, 23.98); the corresponding failure rates in the treatment arms were approx. 12% and 25% respectively.

The applicant provided a separate analysis of cured patients using a revised definition of success (patients meeting the definition of Improvement would be considered failures). The results are consistent with the original conclusion on non-inferiority of anidulafungin to fluconazole at the tested dose levels. See the following table.

Table 5 Global Response Rates for the Microbiologic ITT Population End of IV therapy

	ECALTA N = 127	Fluconazole N = 118	Between group difference	95% Confidence Interval
Per SAP*				
Success	96 (75.6)	71 (60.2)	15.42	(3.85, 26.99)
Revised definition				
Success	86 (67.7)	68 (57.6)	10.09	(-1.98, 22.16)

*: Original Statistical Analysis Plan

Similarly, the results of the given additional analysis according to prior antifungal therapy inclusion criteria of the study are consistent with the primary global response results.

The microbiological success rates are shown in the following table.

Table 6 Pathogen-Level Microbiological Response at End of IV Therapy

	VER002-9 Micro-ITT Population	
Species [a]	**Anidulafungin N/n (%)**	**Fluconazole N/n (%)**
Response (Success %)	**100 mg**	**400 mg**
All Species Eradication Presumed Eradication	**119/135 (88.1)** 92 (68.1) 27 (20.0)	**99/130 (76.2)** 77 (59.2) 22 (16.9)
Candida albicans	77/81 (95.1)	57/70 (81.4)
Non-*albicans* species	42/54 (77.8)	42/60 (70.0)
Candida glabrata	15/20 (75.0)	18/30 (60.0)
Candida tropicalis	13/15 (86.7)	7/11 (63.6)
Candida parapsilosis	9/13 (69.2)	14/16 (87.5)

a: By-species data are presented only for species for which there were 10 or more isolates across the three studies combined. The non-albicans species data therefore includes success rates for species that are not displayed individually (these included 1-2 per species in all cases).
N: Number of patients where the culture is negative for *Candida* species that were originally present at baseline or culture data are not available for a patient with a clinical outcome of cure or improvement.
n: Total number of patients at the end of IV therapy in the Micro ITT population infected with the respective pathogen at baseline

Overall, the success rates for patients infected with the major pathogens *C. albicans* and *C.* glabrata were clearly higher in the anidulafungin arm than in the fluconazole arm. At the end of IV therapy, only 8 (5.9%) of patients treated with anidulafungin had documented persistence of *Candida* infection (2/8 were *C. albicans* infected), compared with 17 (13.1%) of the patients treated with fluconazole (9/13 were *C. albicans* infected). All but 1 of the 8 patients in the anidulafungin arm had candidaemia only at baseline and all 17 patients in the fluconazole arm.

There was no evident trend relating anidulafungin MIC for baseline isolates to the rate of eradication by anidulafungin. However, there were relatively few baseline pathogens with MICs above 0.06, 11/16 were noted for *C. parapsilosis*, these seem to be associated with lower response at the end of IV therapy than for other *C. albicans and C. glabrata*. Also for the fluconazole treatment arm, there was no evident trend relating fluconazole MIC for baseline isolates to the rate of eradication by fluconazole. However, the number of isolates with fluconazole MIC > 8 mg/l was too small for any meaningful comparison. There were relatively few baseline isolates that were non-susceptible to fluconazole (48-h MIC > 8 mg/l) in VER002-9 (32/242 isolates, 13.2%).

Global response at the follow-up time points 2 and 6 weeks are summarised in the following table.

Table 7 Global Success Rates at Follow-up

		Anidulafungin n/N (%)	**Fluconazole** n/N (%)	**Trt Diff †** % (95% CI)
2-WEEK FU	**Micro-ITT Population**	82/127 (64.6%)	58/118 (49.2%)	15.41% (3.14, 27.68)
	Evaluable Population	71/88 (80.7%)	51/76 (67.1%)	13.58% (0.17, 26.98)
6-WEEK FU	**Micro-ITT Population**	71/127 (55.9%)	52/118 (44.1%)	11.84% (-0.60, 24.28)
	Evaluable Population	59/79 (74.7%)	43/69 (62.3%)	12.36% (-2.56, 27.29)

† Treatment difference for anidulafungin minus fluconazole.

Subgroup analyses. Global success rate at the end of IV therapy in the different subgroups of the Micro-ITT population and the mortality are summarised in the following table.

Table 8 Global Success at end of iv therapy for various subgroups (Micro-ITT Population) and Mortality in the study

Subgroup Response	Anidulafungin n (%)	Fluconazole n (%)	Between-Group Difference (%)[a]
All Micro-ITT Patients	96 /127 (75.6)	71/118 (60.2)	15.42 (3.85, 26.99)
DISEASE			
Candidemia	88/116 (75.9)	63/103 (61.2)	14.7 (2.48, 26.91)[b]
Other Forms of Invasive Candidiasis	8/11 (72.7)	8 /15(53.3)	19.39
DEMOGRAPHY			
Age ? 65 years	62/84 (73.8)	45/72 (62.5)	11.31
Age > 65 years	34/43 (79.1)	26/46 (56.5)	22.55
Male	48/65 (73.8)	39/60 (65.0)	8.85
Female	48/62 (77.4)	32/58 (55.2)	22.25
White	73/92 (79.3)	52/87 (59.8)	19.58
Black / African American	14/23 (60.9)	16/25 (64.0)	-3.13
Apache II Score ? 20	82/101 (81.2)	60/98 (61.2)	19.96
Apache II Score > 20	14/26 (53.8)	11/20 (55.0)	-1.15
ANC > 500 cells/mm3	94/124 (75.8)	69/114 (60.5)	15.28
ANC ? 500 cells/mm3	2/3	2/4	
CATHETER STATUS			
No Catheter	16/22 (72.7)	15/21 (71.4)	1.30
Had Catheter and it Was Removed	77/101 (76.2)	53/86 (61.6)	14.61
Had Catheter and it Wasn't Removed	3/4	3/11	
Disease Not Catheter Related[c]	46/64 (71.9)	33/54 (61.1)	10.76
Disease Catheter Related[c], Catheter Removed	47/60 (78.3)	37/55 (67.3)	11.06
Disease Catheter Related[c], Catheter not Removed	3/3	1/9	
Mortality in the Micro-ITT			P-value
Patients who died	29/127 (22.8)[d]	37/118 (31.4)	0.151[e]
Median time to death (Days)	21	14	
Mean time to death (Days)	22.9	22.6	
Time to Death by Study Period			
On therapy ? 3 days	7/127 (5.5)	16/118 (13.6)	
Follow-up	19/127 (15.0)	20/118 (16.9)	

IA = intra-abdominal.

a: Anidulafungin minus fluconazole.

b: Only subpopulation for which 95% confidence interval for between group difference was specified *a priori* to be calculated. Lower bound of confidence interval was greater than zero, indicating superiority of anidulafungin.

c: Relationship as assessed by Investigator at screening

d: Patient 27-003 died after the 6-week follow-up period and is not included in this table.

e: Fishers Exact Test on the proportion of patients who died.

Patients receiving anidulafungin had a higher proportion of global success at the end of IV therapy across age groups (≤65 years vs. > 65 years) and gender. The results in patients with poor (> 20) APACHE II scores were worse in both treatment groups. It is possible, though not certain, that the apparent slight differences observed for sex and racial groups reflect some other underlying confounding factor(s), such as APACHE II scores, but no consistent pattern was detected.
There were too few (<5) neutropenic patients (defined as an ANC ≤ 500 cells/mm^3) at baseline in both arms to allow appropriate conclusions. The same holds for candidiasis at other sites than blood stream (mainly peritoneal fluid and/or IA abscess were involved).

Complications (of the candidaemia) were also evaluated; 3 in each treatment arm developed late complications: in the anidulafungin group 1 patient developed endophthalmitis (was negative at baseline), 1 patient developed a positive *Candida* culture from a normally sterile site and 1 patient had recurrence of *C. albicans* at 6-week FU visit. Similarly, in the fluconazole group 1 patient per each category complication occurred.

Among patients who died in the Micro-ITT population, (anidulafungin: 29/127 deaths, 22.8%; fluconazole: 37/118 deaths, 31.4%), the median time to death was 14 days for fluconazole and 21 days for anidulafungin. In almost all deaths (except for 1-2 per arm) the cause of death was not considered due to candidaemia.

- Supportive studies

Study **VER002-9B** was an open-label, non-comparative, multi-centre additional study of VER002-9 which ultimately enrolled 33 patients. Apart from the lack of a comparator arm, its design was very similar to that of the pivotal study—including, for instance, the provision for switching therapy to oral fluconazole under certain conditions—but it differed in that it permitted the enrolment of patients with certain characteristics that would have rendered them ineligible for pivotal study VER002-9,

specifically: prophylactic administration of fluconazole, itraconazole, or voriconazole for at least 1 week within the 30 days prior to enrolment; current treatment with terfenadine or cisapride; known *C. krusei* infection; known hypersensitivity to azole therapy.

After the pivotal study was closed to enrolment, the Study VER002-9B protocol was amended to allow for enrolment of patients who did not meet the above criteria. Common invasive candidiasis risk factors observed were presence of a central venous catheter, use of broad-spectrum antibiotics, and recent surgery. Approximately half of all patients had invasive candidiasis related to an IV catheter by Investigator assessment. Most (94%) of these patients had the catheter removed as part of the medical management for invasive candidiasis. The primary efficacy endpoint for VER002-9B was like in VER002-9 the global response at the end of IV therapy in the Micro-ITT population.

Results: The global success rate at the end of therapy in the Micro-ITT Population was 21/31 (67.7%) and 12/17 (70.6%) in the evaluable patient population. In the patients with candidaemia the global success rate was 18/28 (64.3). There were only 3 patients with infections at other site and 6 patients with APACHE II Score > 20 with global success rates reported in 3/3 and 3/6 patients respectively. Global success in 30/31 patients who had their catheter removed was 20/30 (66.7).
The global, clinical and microbiological success was sustained at the same level from the 2-week through the 6-week FU visit. Patient-level microbiological success was observed for 80.6% (25/31) patients in the Micro-ITT population at the end of IV therapy.

For the most common baseline pathogens of *C. albicans* (13) and *C. glabrata* (12) microbiological success was approx. 92% (patients where the culture is negative for *Candida* species that were originally present at baseline or culture data are not available for a patient with a clinical outcome of cure or improvement) at the end of IV therapy.

Seven patients (22.6%) died during the study, with a median time to death of 13 days. One patient who received 3 days of anidulafungin developed a late complication of endophthalmitis.
Overall, the global success rate in the Micro-ITT population at EOT was somewhat lower than in the pivotal study.

- Study **VER002-6** was an open-label, Phase II, randomised dose-ranging study in patients (≥18 years of age) diagnosed with invasive *Candida* infections. Three doses were studied (with 40 patients in each dosage arm): maintenance doses of 50, 75 and 100 mg daily (each following a loading dose of twice the maintenance dose (on Day 1). Diagnosis was based on blood or tissue section culture positive for *Candida* and had clinical evidence of infection and (unless they were considered treatment failures) had not exceeded predetermined cumulative doses of other antifungal agents in the previous 7 days. This study contained no provision for switch to oral antifungal therapy. Patients were to be treated until 2 weeks beyond the cure or improvement of clinical signs and symptoms of infection and the (presumed) eradication of the original pathogen. The maximum duration of therapy was not to exceed 42 days. In this study the primary efficacy end point was the global response at 2 week follow-up in the evaluable at follow-up population.

Results: For the primary efficacy end point of global (clinical and microbiological) response at follow-up (FU), success was seen in 72.2% (13/18), 84.6% (22/26) and 83.3% (20/24) of the evaluable at FU population (50 mg group; 75 mg group and 100 mg group respectively). See the following table.

Table 9 Global success in study VER002-6

	Anidulafungin Dose			
Population Timepoint	**50 mg/day n/N (%)**	**75 mg/day n/N (%)**	**100 mg/day n/N (%)**	**All Patients n/N (%)**
Micro-ITT				
End of Therapy	25/37 (68)	30/40 (75)	27/39 (69)	82/116 (71)
2-week Follow-up	14/37 (38)	23/40 (58)	20/39 (51)	57/116 (49)
Efficacy Evaluable				
End of therapy	21/25 (84)	27/30 (90)	25/28 (89)	73/83 (88)
2-week Follow-up[a]	13/18 (72)	22/26 (85)	20/24 (83)	55/68 (81)

a: The evaluable at follow-up population is the primary population

The secondary efficacy analyses of global response at FU and EOT in the Micro-ITT and evaluable at EOT populations were also consistent in that the two higher dose groups had a greater success rate than the lower 50mg dose group. The study was not powered to distinguish among doses for efficacy, and confidence intervals overlapped among dosage groups for both primary and secondary efficacy parameters of global success. The higher responses in the two higher dosage groups, however, suggest a dose response.

Microbiological success at the end of IV therapy in the Micro-ITT population displayed in the following table.

Table 10 Pathogen-Level Microbiological Response at End of IV Therapy: Micro-ITT Population

	VER002-6		
Species [a]	**Anidulafungin N/n (%)**		
Response (Success %)	**100 mg**	**75mg**	**50mg**
All Species	**35/42 (83.3)**	**33/43 (76.7)**	**31/42 (73.8)**
Candida albicans	16/22 (72.7)	16/20 (80.0)	15/20 (75.0)
Non-*albicans* species	19/20 (95.0)	17/23 (73.9)	16/22 (72.7)
Candida glabrata	15/15 (100.0)	7/10 (70.0)	8/11 (72.7)
Candida tropicalis	2/3	4/6	0
Candida parapsilosis	1/1	4/4	5/6

a: By-species data are presented only for species for which there were 10 or more isolates across the three studies combined. The non-albicans species data therefore includes success rates for species that are not displayed individually.
N: Number of patients where the culture is negative for *Candida* species that were originally present at baseline or culture data are not available for a patient with a clinical outcome of cure or improvement.
n: Total number of patients at the end of IV therapy in the Micro ITT population infected with the respective pathogen at baseline

Overall, the global success rate in the Micro-ITT population at EOT supports the choice of the 100 mg daily dose (following a loading dose of 200 mg) for further clinical testing in Phase III trials. The latter global success rate was somewhat lower than in the pivotal study. However, the similarity of the efficacy results of the 100 mg daily dose (following a loading dose of 200 mg) with those from the pivotal study cannot be appropriately assessed, especially, because administration of systemic antifungals within the 7 days prior to enrolment was allowed in contrast to the pivotal study.

Discussion on clinical efficacy

Anidulafungin performed favourably at the recommended dose in the primary efficacy analysis (global response at end of IV therapy in the Micro-ITT population) compared to fluconazole in the pivotal randomised controlled clinical trial in the treatment of patients with ICC (the sought indication) who were primarily non-neutropenic and with candidaemia. At all secondary endpoints, anidulafungin was

at least as effective as fluconazole, although the global response rates to treatments decreased at 2 and 6 weeks FU time points e.g in the Micro-ITT Population to 82/127 (64.6%) and 71/127 (55.9%) resp. in the anidulafungin arm versus 58/118 (49.2%) and 52/118 (44.1%) in the fluconazole arm.

However, a number of caveats have been considered:

-The global success category in the pivotal study is based on the clinical and microbiological success components. Clinical success included cured and improved patients. Separate analyses of cured patients were required in order to gain better insight into the favourable results of anidulafungin versus fluconazole and to draw definitive conclusions in that respect. The provided additional analysis using the revised definition of success (patients meeting the definition of Improvement would be considered failures) showed results which were consistent with the original conclusion on non-inferiority of anidulafungin to fluconazole at the tested dose levels.

- The used comparator fluconazole IV/oral has a narrower activity spectrum (*C. krusei* is intrinsically resistant to fluconazole and *C. glabrata* has reduced susceptibility) than echinocandins and amphotericin B and voriconazole and this dictated that patients with certain non-albicans infections (*C. krusei*) were excluded from the study. On the other hand, the safety profile of fluconazole is more favourable than that of amphotericin B.

-The used dosage of fluconazole (initial 800 mg than 400 mg daily) in this study is the highest approved in many EU countries and is in line with recent consensus publications and guidelines on the treatment of invasive candidiasis in non-neutropenic patients although for seriously ill neutropenic patients with disseminated candidiasis (incl. candidaemia and pulmonary involvement and Candida peritonitis) it might not be a first choice as initial therapy (even at higher doses) [1, 2].

-The chosen non-inferiority margin in this comparative can be criticised as being too wide (20%). However, in the light of the fact that the observed lower limit of the confidence interval for the treatment difference between anidulafungin and fluconazole was greater than zero in the primary analysis and consistent findings across different secondary analyses for the differences between the treatments: the lower limit of the 95% CI was generally positive with a few exceptions- such as for the global success rate in the small subgroup of clinically evaluable patients end of oral therapy (-14.38) and for the global success rate in the clinically evaluable patients -2.56 at the 6 week FU, further discussion is deemed unnecessary.

-The primary endpoint assessment at the end of IV therapy can also be criticised for this indication; assessment at follow-up of at least 2 weeks after treatment would have been preferable. However, FU results at 2 and 6 weeks are also presented in the secondary analyses and seem to be consistent with the efficacy profile in the primary analysis in the end of IV therapy Micro-ITT population which focussed on successful global response (includes clinical and microbiological success).

-Slight imbalance in the number of patients receiving immunosuppressive therapy (larger number in the fluconazole group) was observed. The applicant confirmed with an additional analysis that this did not impact on the global response profile of the Micro-ITT population to the study treatments. The provided additional clarification was satisfactory.

-For a better interpretation of the observed favourable results the subgroup analyses of the clinical and microbiological response were required for the group of patients who received prior systemic antifungal therapy up to 72 hours before entering the study[3] or receiving study treatment and in the group of patients who did not receive relevant antifungal therapy within 14 days before entering the

[1] Büchner T et al. Treatment of severe candida infections in high-risk patients in Germany: consensus formed by a panel of interdisciplinary investigators. Eur J Clin Microbiol Infect Dis. 2002; 21:337-52

[2] IDSA guidelines. "Guidelines for Treatment of Candidiasis" Pappas PG et al. in Clinical Infectious Diseases 2004;38:161-189**.**

[3] In the present study roughly 2/3 of the patients had prior antifungal therapy up to 72 hours when they were entered.

study. The provided additional analysis according to prior antifungal therapy inclusion criteria of the study showed results which were consistent with the primary global response results.

- The very small numbers of *neutropenic* patients preclude reliable conclusions for comparisons between treatment groups. Hence, the efficacy of anidulafungin in this population is not established. Similarly, only, approx. 20% of patients had APACHE II scores>20 and less than 10% of the patients Candida infection at other sites than blood stream (candidaemia was present in more than 90% of patients). This cannot be considered sufficient to reach definitive conclusion on efficacy and optimal dose of anidulafungin in such seriously ill patients or patients infected at other sites than blood stream even when the other small invasive candidiasis studies in the dossier are taken into account. Most patients had only a single baseline species isolated; *C. albicans* (isolated from 62% of patients) and *C. glabrata* (isolated from 20% of patients) were the baseline pathogens most frequently isolated from both the fluconazole and anidulafungin arms. Non-albicans infections other than *C. glabrata* were very limited and insufficient to reach definitive conclusions with regard to the efficacy of anidulafungin against these infections.

To allow appropriate assessment of the optimal dose in patients with severe and complicated invasive candidiasis at other sites than blood stream and including neutropenic patients, comparative data will be necessary.

The underrepresented diagnoses at other sites than blood stream, and almost exclusively non-neutropenic patients in conjunction with the low proportion of subjects with APACHE II scores > 20 dictates a restriction of the generalised claim in Applicant's wording of the indication.

- The provided PK/PD data were considered too limited and do not contribute to adequately characterise the effect of anidulafungin exposure on clinical response and safety parameters, and pharmacokinetics and *in vitro* susceptibility (such as AUC/MIC and time above MIC). Further data on PK/PD to support optimal dosing in a broader indication is needed. The applicant should consider further studies in this area within the context of a post-approval commitment.

- As noted before under PK, in the population pharmacokinetic analysis, the weight effect was within about 30% comparing the extremes of the weight borders (40 and 150 kg) with the normal weight group (70 kg). The applicant was asked to further explore what the impact is on clinical outcome (safety and efficacy) in the pivotal study VER002-9 since such analysis was lacking in the study report. The given additional analyses indicate no adverse impact on efficacy whereas the number of patients on the low end of the weight spectrum (n=12) is too small to allow any indicative conclusions regarding safety. For this outstanding issue the applicant has committed to undertake a specific reporting obligation of the issue in the regular PSURs.

Clinical safety

Safety data has been submitted on invasive candidiasis (ICC) patients exposed to the presently proposed dosage (100 mg maintenance dosage after a loading dose of 200 mg). In addition, safety data has been submitted from the previously sought indication Oesophageal Candidiasis (including the phase III Study VER002-4 in OeC), in which a a 2-fold lower dosage of anidulafungin were used (50 mg after a loading dose of 100 mg**)** The patients with OeC from Study VER002-4, were less critically ill than patients with ICC. Because of the lower dosage and different indication /population, the OeC data are discussed only as supplementary information by way of contrast wherever appropriate. Comparisons between drugs is focused on the integrated ICC population and to a lesser extent on the large OeC population from Study VER002-4. Aspects of safety that may be peculiar to anidulafungin are discussed below under "Special Safety Topics".

- Patient exposure

The source of the main data sets for safety analysis is displayed in the following table.

Table 11 Main Datasets for Safety Analysis

Dataset	Contributing Studies	N
ICC (100 mg)	VER002-9, VER002-9B, VER002-6‡,	204 anidulafungin; 125 fluconazole*
OeC (50 mg)	VER002-4	300 anidulafungin; 301 fluconazole†

*oral and IV(400 mg); †oral only (200 mg); ‡ 100 mg arm only

The median duration of exposure to the recommended dose anidulafungin in the ICC studies was 14 days which was comparable to that in the pivotal OeC study using the 2-fold lower dose of anidulafungin. Altogether in the Phase II/III ICC programme, 5 patients (not from the pivotal study) were exposed to IV anidulafungin for more than 42 days, with the longest duration of exposure in any patient being 90 days. In the pivotal ICC study there were no patients exposed to anidulafungin for more than 35 days (only 3 were treated 29-35 days).

Table 12. Exposure to recommended anidulafungin dose (IV) and fluconazole (oral and IV) in ICC Phase II/III studies

	ICC	
	Anidulafungin 100 mg	**Fluconazole 400 mg IV**
N=	204	125*
≤ 14 days	128 (62.7)	90 (72.0)
> 14 days	76 (37.3)	35 (28.0)
Mean (days) ± SD	13.5 ± 6.25	12.2 ± 6.51
Median	14.0	11.0
Range (days)	1-38	1-37

*This table shows exposure to drug of randomisation only.
Note that exposure in days is not always equivalent to number of doses administered
Doses shown are maintenance doses, equal to half the loading dose.
For fluconazole, dose was also adjusted for renal insufficiency.

The demographic characteristics were well balanced between the anidulafungin and fluconazole treatment groups (with the exception of immunosuppressive therapy, see under efficacy above). The racial composition of the populations varied in accordance with the location of the study sites. Because anidulafungin is not metabolised, and does not appear to affect the metabolism of other drugs, exposure would not be expected to vary by genetic factors which may vary with race.

- Adverse events

Proportionally, more all-causality AEs were reported among ICC patients than among OeC patients (98.5% and 79.7% of patients treated with anidulafungin respectively). This is not unexpected as ICC patients were more critically ill, than OeC patients. A few AEs occurred with greater frequency (≥ 5% difference between groups) among patients randomised to anidulafungin (nausea, vomiting and dyspnoea) or to fluconazole (urinary tract infection, anaemia, abdominal pain, thrombocytopenia, anxiety and back pain).

Among ICC patients, treatment-related AEs occurred in 27.5% of patients treated with anidulafungin (vs. 26.4% for fluconazole). This is higher than in the OeC patients [43/300 (14.3%)] exposed to lower doses of both antifungals. It is not likely that the higher doses of both anidulafungin and fluconazole used in the ICC population have resulted in more treatment-related AEs, since such a trend was not noted in anidulafungin dose-ranging Study VER002-6.

Table 13 Adverse Events and Serious Adverse Events, n, (%)

	ICC	
	Anidulafungin 100 mg IV	**Fluconazole 400 mg IV**
N=	204	125
Patients with at least 1 AE (all causality)	201 (98.5)	122 (97.6)
Patients with at least 1 AE (treatment-related)	56 (27.5)	33 (26.4)
Patients with at least 1 SAE (all causality)	102 (50.0)	102 (50.0)
Patients with at least 1 SAE (treatment-related)	5 (2.5)	2 (1.6)

Relatively few treatment-related AEs occurred in more than 1% of either treatment group, and only diarrhoea (anidulafungin ICC) and ALT increased (fluconazole ICC) occurred in more than 3% of patients in any treatment group, see the following table. Altogether for anidulafungin-randomised patients, there were 46 Preferred AE Terms reported for the ICC population (only 4 of which were reported by more than 1 patient).

Within the anidulafungin group of the integrated ICC population, 41 of the 204 patients (20.1%) changed therapy from anidulafungin to oral fluconazole as permitted by protocol 34 from Study VER002-9 and 7 from Study VER002-9B. For the purposes of safety analysis, these patients were analysed as members of the anidulafungin group even if an AE was reported after the change in therapy. However, when analysis was confined to patients who only received IV anidulafungin, the safety profile remains essentially unchanged

Table 14 Treatment-Related AEs in the ICC (occurring in ≥ 1% of patients)

	ICC*	
	Anidulafungin 100 mg	**Fluconazole 400 mg IV**
N=	204‡	125
Patients with at least 1 AE	56 (27.5)	33 (26.4)
Diarrhoea	7 (3.4)	2 (1.6)
Hypokalaemia	6 (2.9)	3 (2.4)
Blood Alk Phos inc.	4 (2.0)	5 (4.0)
ALT inc.	4 (2.0)	4 (3.2)
Flushing	3 (1.5)	2 (1.6)
Blood bilirubin Inc.	3 (1.5)	1 (0.8)
Hypomagnesaemia	3 (1.5)	1 (0.8)
Convulsion	3 (1.5)	0
Headache	2 (1.0)	1 (0.8)
GGT inc.	2 (1.0)	0
AST Inc.	2 (1.0)	3 (2.4)
Rash §	4 (2.0)	1 (0.8)
Blood creatinine inc.	2 (1.0)	0
Coagulopathy	2 (1.0)	0
ECG QT prolonged	2 (1.0)	0
Hyperkalaemia	2 (1.0)	0
Platelet count dec.	2 (1.0)	0
Pruritus	2 (1.0)	0
Thrombocytopenia	2 (1.0)	0
Nausea	1 (0.5)	1 (0.8)
Neutropenia	0	0
Dyspepsia	0	0
Leukopenia	0	0
Vomiting	1 (0.5)	0
Pyrexia	0	1 (0.8)
Hepatic enzyme increased	1 (1.1)	5 (4.0)
Liver function test abnormal	1 (0.5)	4 (3.2)
Anaemia	0	2 (1.6)
Chills	0	2 (1.6)

		ICC*
Deep vein thrombosis	0	2 (1.6)
Dizziness	0	2 (1.6)

* Studies VER002-9, -9B and 6 (100 mg arm only). Includes patients from Study VER002-9 whose therapy was changed from IV anidulafungin to oral flucaonzole. ‡Includes 41 patients who switched to oral fluconazole.

§ Also includes 'rash papular' and 'rash macular'.

A pronounced higher incidence of gastrointestinal AEs was observed in the anidulafungin arm compared with the fluconazole arm with nausea in 44 patients (21.6%) vs. 14 (11.2%) and vomiting in 33 (16.2%) vs. 12 (9.2%). Due to noted imbalance in the frequencies of nausea and vomiting it was judged appropriate to consider nausea and vomiting as being common ADRs.

With respect to the muscular safety profile of anidulafungin, no specific risk minimisation activities or warning in the SmPC is necessary since there is no compelling evidence to suggest that anidulafungin is associated with CPK elevations or muscular symptoms over and above what might be expected in the target population

The AE profile of anidulafungin as observed in the Phase I/SP was roughly similar to that described above, however, the serious AEs e.g the hematological and cardiovascular AEs were practically absent, most likely because these subjects did not have similar underlying disease conditions and concomitant medication as in the Phase II/III patient population. Furthermore, several events were reported in the clinical pharmacology studies at incidences of >0.5% which were not commonly reported in the Phase II/III studies. These included infusion site erythema, dizziness, infusion site pain, abdominal pain, dyspnoea, visual disturbance, infusion site swelling and photophobia. Infusion reactions and elevated liver enzymes, which were noted in some of these studies, are discussed below.

Special safety topics

Infusion-associated adverse events: Results from Phase I (study XBAE) suggested that infusion-related reactions could be minimized if anidulafungin was dosed at a rate of 1.1 mg/min and a concentration of 0.5 mg/ml. This was implemented in clinical Phase II/III studies. The incidence of *infusion-associated adverse events* in the latter studies was very low. The present SPC recommends an even slightly lower infusion rate. Using MedDRA terms of *flushing, hot flush, urticaria, chills, dizziness, feeling hot* and *hyperhidrosis* as search criteria, 4 of 204 (2.0%) anidulafungin-randomised and 5 of 125 (4.0%) fluconazole-randomised patients experienced potentially infusion-related AEs. No treatment related thrombophlebitis cases were noted in the ICC studies in the anidulafungin treated patients.

Hepatotoxicity. As noted in the previous submission for the OeC indication, at dosage regimens up to 100 mg daily, there was no apparent effect of anidulafungin on serum concentrations of *liver enzymes*. However, asymptomatic and reversible elevation of transaminases were observed in some of the Phase 1 studies. In addition, a dose-response effect on ALT, AST and GGT was suggested by data in dose-escalation Study VER002-5 (using anidulafungin loading/ maintenance doses of 150/75, 200/100 and 260/130 mg -each for 10 days). All 8 events in this study were associated with administration of the highest dose. In the presently evaluated patients with ICC, AEs of hepatobiliary nature (by Standard MedDRA Query) were reported at similar frequency in the anidulafungin and fluconazole treatment groups. Cholestasis (moderate) possibly related to anidulafungin was reported (day 9) in the pivotal ICC study in a patient with myelogenous leukaemia but the patient was on several confounding concomitant medications.

A Hepatic Expert Report prepared by an external hepatologist reviewed any cases of patients from Studies VER002-4 , -5 , -6 , -7 , -9 , -11 , -12 and -15 who experienced both elevations in ALT (> 2 × ULN) and elevations in bilirubin (1.5 × ULN) that occurred simultaneously or within 1 month afterwards. Ten such patients from anidulafungin treatment groups and 8 from fluconazole groups were identified and reviewed. The report concluded that the "risk of irreversible liver injury from short term treatment (< 2 weeks) with anidulafungin appears to be low, and in line with the risk from

systemic fluconazole treatment in the patient populations studied". Although the risk appears low, the proposed SPC warns for the potential for hepatic effect when treating patients with anidulafungin.

QT prolonged. No non-clinical evidence of a clinical risk for *QTc interval changes* was identified. Monitoring of QT segment changes was incorporated into the large Phase II/III studies. ECGs were done at screening and again (within 3 hours of drug infusion) on day 3 (Studies VER002-9,-9B and -4) or day 6 (Study VER002-6). These were read not only by the investigator, but also in a blinded fashion by a central reference cardiac laboratory, which after unblinding at study completion issued a dedicated QT report for each of these studies. There were no notable differences between anidulafungin-treated patients and fluconazole-treated patients in the mean change from baseline in QTc interval or in the distribution of patients among QTc interval changes from baseline. In the ICC studies, 4 patients were reported with an adverse event of "*electrocardiogram QT prolonged*" (3 from the anidulafungin and 1 in the fluconazole group, all from Study VER002-9). Two of these AEs (both in the anidulafungin group) were judged to be at least possibly related to the study drug. However, the central cardiac laboratory review failed to confirm QTc prolongation in any of the 3 anidulafungin-treated patients.

Also analysis using relevant Standard MedDRA Queries (SMQs) in the ICC safety data revealed little difference between the two treatment groups in the frequencies of any AEs that might have been related to an otherwise unrecognised *torsade de pointes*. Further monitoring of QT prolongation risk will be conducted in the PMS.

Pigmentation Anidulafungin binding to melanins may have consequences on different melanin pigmentation in the patient (e.g. In the skin and eyes; ADRs/AEs as given in section 4.8 of the SPC: eye pain, visual disturbance, vision blurred). At this stage, there does not seem to be a clinically relevant risk of toxicity associated with anidulafungin binding to melanin and this issue will be further monitored as part of routine pharmacovigilance.

Seizures. Anidulafungin did not lower the seizure threshold in animals. No seizures were noted among healthy volunteers in Phase 1 studies, but a number of patients in Phase 2/3 studies were reported to have seizures while on treatment with anidulafungin. All of these appear to have had co-morbidities that could explain the event, although 5 were judged by the investigator to be at least possibly related to the study drug. It remains unclear to what extent, if any, anidulafungin might precipitate a seizure or lower the seizure threshold in susceptible individuals.

Other issues The data in the clinical studies are insufficient to conclude on the occurrence of increased cholesterol, disturbances in water balance, haemolysis, and phototoxicity which were noted in animal toxicity testing.

- Serious adverse events and deaths

SAEs in general occur at comparable rates between anidulafungin and fluconazole patients when compared within indications or within studies. For both anidulafungin- and fluconazole-randomised patients, treatment-related SAEs in the pivotal ICC study occurred at rates of 2 /131 (1.5%) and 2 /125 (1.6%) respectively.

Treatment-related SAEs were more common in the ICC than in the OeC (Study VER002-4) population with rates of 0.7% in both groups: Hepatic necrosis (patient 13008) and maculo-papular rash (patient 10007) in the anidulafungin arm versus pancytopenia (patient 04065) and acute renal failure (patient 04063) in the fluconazole arm.

Eleven patients exposed to anidulafungin in the Phase I/SP studies were reported as having SAEs, none of which was judged drug-related and all but 1 of which occurred in Study VER002-12, conducted in critically ill immunocompromised children.

Deaths. Mortality was relatively high in the ICC studies, reflecting the serious nature of the disease: 48 of 204 (23.5%) patients randomised to anidulafungin and 39 of 125 patients who received

fluconazole (31.2%) died. In OC study VER002-4, in contrast, the death rate was in the 6 to 8% range.

Among patients randomised to anidulafungin, all but 2 AEs that resulted in death were judged to be unrelated or unlikely to be related to study drug (convulsions in Patient 011-001 in Study VER 002-6, and hepatic necrosis in Patient 013-008 in Study VER 002-4).

In the Phase I Study VER002-12 conducted in critically ill immunocompromised children, 3 deaths were reported (2 respiratory failure, 1 recurrent leukaemia). These deaths occurred from 21 to 99 days after the last anidulafungin treatment. None was judged drug-related.

- Laboratory findings

Haematology and chemistry laboratory testing reveal no pattern in the Phase II/III data that suggested an anidulafungin effect. However, in Phase I Study VER002-5, a dose escalation study using loading/maintenance doses of 150/75, 200/100 and 260/130 mg (each for 10 days) there appeared to be a dose-dependent trend for increases in ALT, AST, and GGT.

- Immunological events

In non-clinical studies, following repeated dosing it was not immunotoxic in assays to evaluate humoral immunity and proliferative capability, and did not cause alterations in lymphocyte populations in the spleen or thymus of rats.

Overall, there was no apparent effect of anidulafungin on hematology laboratory parameters in the clinical trials. Treatment-related maculo-papular rash (SAE) in the OC (Study VER002-4) population has been reported

- Safety in special populations

About a third of patients in the ICC studies were *65 years of age or older*. Proportionally more severe AEs were reported among elderly patients, but their frequency was similar to that of younger patients, except that respiratory distress was reported by more patients aged 65 and older.

AEs were reported by proportionally more patients with derangements of liver function; no such pattern was noted in patients with renal impairment. The dose of anidulafungin does not need to be adjusted for *renal or hepatic dysfunction*.

Women who were *pregnant* or who might become pregnant were excluded from the clinical trials, and no events of pregnancy were reported during the clinical programme. The SPC recommends such use only if the potential benefit is felt to outweigh the risk to the foetus.

Minimal data are available on *overdosage*. The highest loading/maintenance dose in the clinical programme was 260/130 mg (Study VER002-5). In another study, a dose of 400 mg was inadvertently administered to a patient as a loading dose (instead of 200 mg), and was followed by a minimal and *transient rise in total bilirubin*.

There is limited clinical experience with anidulafungin in *children* (study VER002-12). The latter study evaluated the pharmacokinetics of two dose levels and safety of anidulafungin after i.v. administration to 24 immunocompromised children aged 2–17 years with neutropenia. Pharmacokinetic data suggest that a maintenance dose of 1.5 mg/kg/day in children corresponds to a maintenance dose of 100 mg/day in adults, but efficacy in children has not been assessed and safety data are limited. The safety of the 1.5 mg/kg dosage group is relevant in the context of the dose level recommended for adults. The applicant is encouraged to pursue development of this echinocandin for use in paediatric patients (FUM).

- Safety related to drug-drug interactions and other interactions

Anidulafungin demonstrated a low potential for drug-drug interactions, and was well tolerated when co-administered with ciclosporin, protease inhibitors, reverse transcriptase inhibitors, systemic corticosteroids, organ transplant immunosuppressants, or rifampicin-containing medications.

- Discontinuation due to adverse events

Only Studies VER002-9, -9B and -11 distinguished between "discontinuation from study" and "discontinuation from study medication". In the other Phase II/III studies, only data on "discontinuation from study" were collected.

In the ICC studies (VER002-9 and -9B) more patients in the anidulafungin group completed treatment with study medication than in the fluconazole group (74.4% versus 61.6%). The most common reasons for discontinuation from study medication were "Adverse event" and "Worsening clinical status", and both of these were more commonly reported for patients randomised to fluconazole (approx.17% vs. 10% in the anidulafungin group). Study discontinuation due to death in the pivotal ICC study was at higher rate in the fluconazole arm (approx. 30% vs. approx. 22% in the anidulafungin group).

Discussion on clinical safety

The safety database for the sought indication is rather limited. The safety profile of anidulafungin in patients with ICC is similar to that of fluconazole, but respiratory distress (occurring in 3.3% anidulafungin patients vs 0.7% fluconazole patients), and dyspnoea (occurring in 5.8% anidulafungin patients vs 1.4% fluconazole patients) was an exception (see Risk Management Plan below). Infusion reactions are a possible side effect of anidulafungin, but remain at an acceptable level by adherence to the administration recommendations in the proposed SPC. Anidulafungin may be associated with hepatotoxicity, though the incidence was very similar to that of fluconazole. It remains unclear to what extent anidulafungin might precipitate a seizure or lower the seizure threshold in susceptible individuals.

Only very few cases of QT prolongation were reported and the events were not confirmed as QT prolongation by central reference cardiac laboratory review of the ECGs. However, for reassurance, data from proactive monitoring for a thorough QT prolongation in the larger clinical studies were reviewed. This provided sufficient clarification and reassurance in relation to the risk of QT interval prolongation. It is not likely that anidulafungin is associated with this risk at the recommended dose level in the target population. Further monitoring of this risk will be conducted in the post-marketing stage.

Long-term safety data on anidulafungin are limited. The Applicant should perform a close post-marketing surveillance together with a strict safety assessment of all future trials with particular attention paid to long-term safety data and to safety issues such as putative hepatotoxic reactions and allergic reactions related to potential long-lived anidulafungin degradates. The data should be collected and submitted as part of the PSURs.

Only limited short-term paediatric data are available from the small pharmacokinetic study VER002-12. So far, these data give no reason for additional concern compared to adult patients. However, the limited data do not allow definitive assessment of the safety and efficacy of anidulafungin in children. The applicant will further develop this echinocandin for use in paediatric patients.

The information included in the SmPC outlines the safety profile of anidulafungin as documented in the clinical studies.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Table 15 Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important Identified Risks		
Infusion-associated AEs	• Routine/enhanced pharmacovigilance. • Additional data collection in planned studies: -Pediatric candidemia study (A8851008); -Candidemia/invasive candidiasis study in adult and elderly patients (A8851011) -ICU special population Candidemia/ invasive candidiasis study	Wording in SmPC Sections 4.2, 4.4, 4.8, and 6.6
Hepatobiliary AEs	• Routine/enhanced pharmacovigilance. • Additional data collection in planned studies: -Pediatric candidemia study (A8851008); - Candidemia/invasive candidiasis study in adult and elderly patients (A8851011) -ICU special population Candidemia/ invasive candidiasis study -Post-marketing surveillance study of hepatotoxicity	Wording in SmPC Sections 4.2, 4.4, and 4.8
Important Potential Risks		
Convulsions	• Routine/enhanced pharmacovigilance. • Additional data collection in planned studies: -Pediatric candidemia study (A8851008); - Candidemia/invasive candidiasis study in adult and elderly patients (A8851011) -ICU special population Candidemia/ invasive candidiasis study	Wording in SmPC Section 4.8
Anesthetic exacerbation of infusion-associated AEs	• Routine/enhanced pharmacovigilance. • Additional data collection in planned studies: -Pediatric candidemia study (A8851008); -Candidemia/invasive candidiasis study in adult and elderly patients (A8851011) -ICU special population Candidemia/ invasive candidiasis study	Wording in SmPC Sections 4.4 and 5.3
QT Prolongation/*Torsade de Pointes*	• Routine pharmacovigilance	None
Important limited/missing information		
Children and Adolescents	• Routine pharmacovigilance • Additional data collection in a Pediatric candidemia study (A8851008)	Wording in SmPC Sections 4.2 and 5.2
Pregnancy and Lactation	• Routine pharmacovigilance	Wording in SmPC Sections 4.6 and 5.3
Neutropenic Patients	• Routine pharmacovigilance	Wording in SmPC

	• Additional data collection in planned studies: -Pediatric candidemia study (A8851008); -Candidemia/invasive candidiasis study in adult and elderly patients (A8851011) -ICU special population Candidemia/ invasive candidiasis study	Section 5.1
Elderly	• Routine pharmacovigilance. • Additional data collection in planned studies: -Candidemia/invasive candidiasis study in adult and elderly patients (A8851011) -ICU special population Candidemia/ invasive candidiasis study	Wording in SmPC Sections 4.2 and 5.2
Resistance to anidulafungin	• Additional data collection: -Antifungal surveillance programs (ARTEMIS, SENTRY) -Planned Phase 4 clinical studies (A8851008 Pediatric candidemia study; A8851011 Candidemia/Invasive candidiasis in adult and elderly patients; ICU special population Candidemia/ invasive candidiasis study)	Wording in SmPC Section 5.1

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

There are no major non-clinical reservations about the proposed use of anidulafungin, provided the duration of treatment is limited in accordance with the recommendation defined in the SPC.

Efficacy

The CHMP considered the provided efficacy data to be too limited to be extrapolated to the general indication in the treatment of patients with invasive candidiasis including candidaemia. Regarding the use in invasive candidiasis, an insufficient number of neutropenic patients have been studied; in addition, the study population comprised a limited number of patients with deep tissue candida infections or with abscess-forming disease. A restriction in the wording of the indication is therefore recommended.

Safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

Risk-benefit assessment

The overall B/R of ECALTA is positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of ECALTA in the

> "Treatment of invasive candidiasis in adult non-neutropenic patients.
>
> ECALTA has been studied primarily in patients with candidaemia and only in a limited number of patients with deep tissue *Candida* infections or with abscess-forming disease (see section 4.4 and section 5.1)."

was favourable and therefore recommended the granting of the marketing authorisation.