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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Eraxis™ / Ecalta® / Anidulafungin

PROTOCOL NO.: A8851022

PROTOCOL TITLE: Efficacy and Safety of Eraxis™/ Ecalta® (Anidulafungin) Compared to Cancidas® (Caspofungin) in Patients With Candida Deep Tissue Infection

Study Centers: A total of 15 centers enrolled and randomized subjects. This study was conducted at 4 centers in Belgium, 3 centers in the Netherlands, 2 centers each in Portugal and in the United States, 1 center each in Bulgaria, Canada, Switzerland and in the Russian Federation.

Study Initiation and Final Completion Dates: 30 April 2009 to 04 June 2012. This study was terminated prematurely due to slow enrollment.

Phase of Development: Phase 3b

Study Objectives:

Primary Objective: To assess the efficacy of anidulafungin and caspofungin with respect to the overall global response (clinical and microbiological success) at the end of treatment (EOT) in subjects with a confirmed diagnosis of deep tissue infection due to *Candida* species.

Secondary Objectives:

- To evaluate the safety profile of anidulafungin and of caspofungin in this population.
- To evaluate the clinical and microbiological efficacy of anidulafungin and of caspofungin at various time points.

METHODS

Study Design:

This was a Phase 3b, comparative, double-blind (third-party unblinded), double-dummy, randomized, multicenter, multinational study of anidulafungin versus caspofungin for the treatment of culture confirmed deep tissue infection due to *Candida* species in subjects ≥16 years of age.

Subjects with a high suspicion of deep tissue *Candida* infection may have been enrolled and had study treatment initiated, pending culture confirmation. Subjects in whom culture confirmation was not obtained within 96 hours after enrollment were to be discontinued from study treatment (but were to remain in the study for safety assessment only) and treated according to local standard practice. These subjects did not count toward the sample of evaluable subjects.

Enrolled subjects were stratified according to their Acute Physiology and Chronic Health Evaluation (APACHE) II score (≤20 or >20). Following stratification, subjects were randomized in a 2:1 fashion to receive either anidulafungin or caspofungin.

The duration of subject participation was based on the subject's clinical response, as judged by the Investigator. Study treatment was to be administered for at least 14 days following resolution of clinical signs and symptoms, and after the last positive culture for *Candida* species. A maximum of 42 days of treatment was allowed.

Assessments were performed at multiple time points during the study, including Day 10 of treatment, EOT, and the 2-week and 6-week Follow-up (FU) Visits. The study concluded 6 weeks after the last dose of study drug. Overall, subjects may have been involved in the study for a maximum of 12 weeks (Table 1).

Table 1. Schedule of Activities

Parameters	Screening[a]	Treatment Initiation (Day 1)	Daily Through EOT	Every 3 Days Through EOT	Day 10	End of Treatment (EOT)[b]	Follow-Up Visits Week 2 (±2 Days) Week 6 (±1 Week)[c]
Informed consent	X						
Confirm eligibility, assign study number	X		X[d]				
Randomization		X					
Medical, surgical, and medication history	X						
APACHE II	X[e]		X[f]			X[f]	
Complete physical examination[g]	X						
Brief physical examination[h]		X[i]				X	X
Signs and symptoms of *Candida* infection	X	X		X	X	X	X
Temperature	X	X	X			X	X
Fundoscopic examination[j]	X[k]			X[l]		X[l]	X[l]
Serum or urine pregnancy test[m]	X[m]					X[m]	X[m]
Blood cultures	X[n]		X[o]			X	X
Specimen cultures	X[p]			X[q]		X[q]	X[q]
Hematology[r]	X			X		X	X
Chemistry panel[s]	X			X		X	X
Child-Pugh score	X		X[t]				
(1,3)-β-D-glucan[u]	X			X[u]		X	
Study drug		X	X			X	
Concomitant medications	X	X	X			X	X[v]
Assessment of clinical response					X		
Assessment of clinical and microbiologic success						X	X
Adverse events		X	X			X	X

AE = adverse event; APACHE = Acute Physiology and Chronic Health Evaluation; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; EOT = end of treatment; IEC = Independent Ethics Committee; IRB = Institutional Review Board; RBC = red blood cell count; WBC = white blood cell count.

a. Screening procedures/assessments were to be completed before the first dose of study drug.

b. EOT procedures were to be completed for all subjects who discontinued from the study, regardless of the reason.

c. For subjects who were withdrawn from study treatment (for any reason), only the following activities at the 2-week and 6-week Follow-Up Visits were to be performed: brief physical examination, assessment of temperature, collection of a blood sample for hematology and chemistry panel, recording of AEs since the last study visit, and recording of the use of systemic antifungal medications since the last study visit. If the subject experienced an AE during the follow-up period, all concomitant medications the subject was receiving at the time of the AE were to be recorded.

d. Confirmation of positive culture results for *Candida* species was required within 96 hours after enrollment.

Table 1. Schedule of Activities

e. An APACHE II score was to be calculated at any time between screening and randomization. It was acceptable to use an APACHE II score calculated within 48 hours before randomization, provided, in the Investigator's judgment, the subject's condition had not changed to the extent that a recalculation of the APACHE II score would be expected to yield a different result.

f. The APACHE II score, if calculated for clinical reasons, was recorded.

g. A complete physical examination was to be performed within 72 hours before the first dose of study drugs.

h. A brief physical examination was a focused physical examination relevant to the subject's condition and progress, as determined by the Investigator, and included an assessment of vital signs. Other examinations may also have been performed at the discretion of the Investigator.

i. A brief physical examination was to be performed on the first day of administration of study drugs. However, if a complete physical examination was performed within 24 hours before the first dose of study drugs, then a brief physical examination was not required.

j. Fundoscopic examination for determination of the presence or absence of endophthalmitis was to be performed by an ophthalmologist, unless it was not possible for practical reasons, in which case they may have been performed by a non-ophthalmologist physician.

k. For a subject enrolling on the basis of *Candida* endophthalmitis, the results of a fundoscopic examination performed within 96 hours prior to enrollment may have been used in place of the screening fundoscopic examination. If the subject was not being enrolled on the basis of *Candida* endophthalmitis, then a baseline fundoscopic examination was to be performed prior to the first dose of study drugs. However, if, for practical reasons, a baseline fundoscopic examination could not be obtained prior to Day 1, the examination may have been performed within 48 hours after the first dose of study drugs.

l. This was to be completed if the baseline fundoscopic examination was positive for findings consistent with *Candida* endophthalmitis.

m. In women of childbearing potential, a serum or urine pregnancy test was to be performed at the time of screening (before the first dose of study drugs), at the End of Treatment, and at the 6-Week Follow-Up Visit. Additional testing may also have been performed as requested by the IRB/IEC or as required by local regulations.

n. Screening blood cultures were to be obtained on all subjects.

o. Blood cultures were to be repeated daily until negative twice consecutively, and then repeated at least once weekly thereafter while on study drugs. Blood cultures collected while on study drugs were to be obtained before administration of the dose.

p. For a subject enrolling on the basis of a documented or suspected nonblood tissue culture for *Candida* species obtained within 96 hours before enrollment, a specimen collected at Screening was not required. If a subject was enrolled on the basis of a blood culture only, then a specimen culture at Screening may have been collected only if clinically indicated.

q. A specimen culture was to be obtained, as clinically indicated.

r. Hematology panel: RBC, hemoglobin, hematocrit, WBC (including differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelets.

s. Chemistry panel: AST, ALT, alkaline phosphatase, bilirubin, BUN, creatinine, sodium, potassium, bicarbonate, chloride, albumin, and nonfasting glucose.

t. During the study treatment period, calculation of the Child-Pugh score was to be repeated, as frequently as clinically indicated, in subjects who experienced a significant change in liver function (as judged by the Investigator). The newly calculated score was to be communicated to the unblinded pharmacist for the purpose of adjusting the dose of caspofungin (according to the caspofungin product label), if necessary.

u. A blood sample for (1,3)-β-D-glucan assay was to be obtained at Screening, then repeated every 3 days until 2 successive negative fungal cultures from monitored samples (blood or other sites) were obtained. A blood sample for (1,3)-β-D-glucan assay was also obtained at EOT.

v. Only antifungal medications and their indication for use (eg, for prophylaxis or treatment) were required to be reported during the follow-up period, unless the subject experienced an AE during this time, in which case all concomitant medications the subject was receiving at the time of the AE were to be recorded.

Number of Subjects (Planned and Analyzed): It was planned to recruit sufficient subjects to ensure that there were 45 subjects with confirmed deep tissue *Candida* infection suitable for inclusion in the modified intent-to-treat (mITT) population.

At the time of study termination, 41 subjects were randomized and 39 subjects were treated with at least 1 dose of study drug (26 subjects received anidulafungin and 13 subjects received caspofungin).

Diagnosis and Main Criteria for Inclusion: Male or female subjects ≥16 years of age with a diagnosis of deep tissue Candida infection, defined as growth of *Candida* species from a culture specimen obtained from a normally sterile site accompanied by signs and symptoms of infection, and expected hospitalization for at least 14 days were eligible to be enrolled in the study. Exclusion criteria included pregnancy or breast feeding or planning to become pregnant during the study, recent treatment with one of the study drugs over the previous 30 days, allergy to either study drug or to this class of drugs, significant liver dysfunction, and suspected *Candida* osteomyelitis, endocarditis, meningitis or any other infections of the central nervous system.

Study Treatment: Subjects were randomized to receive either intravenous (IV) anidulafungin or IV caspofungin. Subjects were randomized to 1 of the 4 treatment groups listed below, with an overall randomization of 2:1 (active anidulafungin to active caspofungin):

- Group 1: Active anidulafungin followed by placebo caspofungin.
- Group 2: Placebo caspofungin followed by active anidulafungin.
- Group 3: Active caspofungin followed by placebo anidulafungin.
- Group 4: Placebo anidulafungin followed by active caspofungin.

On Day 1, subjects randomized to active anidulafungin received a loading dose of 200 mg. The loading dose of anidulafungin, consisted of the administration of 2 consecutive infusion solutions of anidulafungin 100 mg (200 mg total), each delivered over 1.5 hours. No dose adjustment was required for subjects with any degree of renal or hepatic insufficiency, subjects using concomitant medications, or those in other special patient populations. These subjects also received a loading dose of placebo caspofungin in the form of the corresponding matching infusion fluid volume.

On Day 1, subjects randomized to active caspofungin received a loading dose of 70 mg. These subjects also received a loading dose of placebo anidulafungin in the form of the corresponding matching infusion fluid volume.

Efficacy Endpoints: Primary Endpoint: The primary efficacy endpoint was the global response at EOT in the mITT population.

Global response was based on the following definitions:

- Success: A subject was categorized as having successful response if there was a clinical response of cure or improvement and microbiologic eradication or presumed eradication.

- Failure: A subject was categorized as having an unsuccessful response if there was a clinical response of failure and/or unsuccessful microbiologic response (persistence or new infection at FU or relapse at FU).

- Indeterminate: A subject was categorized as indeterminate if there was a clinical response of indeterminate and/or microbiologic response of indeterminate and there was neither clinical response of failure nor unsuccessful microbiologic response (persistence or new infection or relapse).

Secondary Endpoints:

- Global response at the 2-week and 6-week FU Visits in the mITT population. A global response determination of failure at any time point was carried forward programmatically to all subsequent visits.

- Response based on clinical cure and microbiological success (eradication or presumed eradication) at EOT, and 2-week and 6-week FU Visits in the mITT population.

- Clinical response at Day 10.

- Rates of relapse (microbiologic response of recurrence) at the 2-week and 6-week FU Visits.

- Rates of new infection (microbiologic response of new infection), with an organism not identified at Baseline, at the 2-week and 6-week FU Visits.

- Time to first negative blood culture (subjects who had a positive blood culture in the period 48 hours prior to first dose of study drug).

- Time to death.

- All cause mortality during study therapy and FU Visits.

Safety Evaluations: Adverse events (AEs), including potential cases of drug-induced liver injury, clinical laboratory measurements, microbiologic determinations, physical examinations, and signs and symptoms of *Candida* infection were assessed throughout the study.

Statistical Methods: The study was descriptive in nature and not powered to stand alone to provide conclusive evidence of efficacy and/or safety. No formal statistical tests of hypothesis were performed. Three data sets were analyzed:

- The safety analysis set consisted of randomized subjects who received at least 1 dose of study drug. Subjects were analyzed according to treatment received, ie, as treated.

- The mITT population consisted of all subjects who received at least 1 dose of study drug and who had a positive culture for *Candida* species isolated from cultures obtained within 96 hours before study entry or at Screening. Due to logistical issues at the local level and the timing of screening activities/treatment initiation, subjects whose qualifying culture for study entry was collected just outside the 96-hour window (ie, within 5 days) were included in the mITT population. Note that the Sponsor's decision to expand the 96-hour window was made prior to database lock and unblinding. The mITT population was the primary efficacy analysis population.

- The per protocol (PP) analysis set consisted of the subjects in the mITT population who, in addition:

    - Received total antifungal treatment for a minimum duration of 14 days, unless declared a clinical and/or microbiologic failure.

    - Had not received >48 hours of systemic antifungal therapy (for treatment of current *Candida* infection) prior to the first dose of study drug.

    - Did not have a prosthetic device and/or vascular catheter (including central venous catheter or an implantable port) at a suspected site of infection, unless the device was removed at study entry or soon after first dose of study drug.

    - Had not taken >1 day of protocol prohibited antifungal therapy concomitant with study therapy, unless declared a clinical and/or microbiologic failure.

    - Had reached the 6-week FU Visit, unless the subject died or withdrew consent prior to 6-week FU.

    - Did not have any protocol violations that could have had an impact on the efficacy endpoints.

Global response was estimated, and differences and confidence intervals (CIs) were calculated. Relapse rate and the rate of new infection were analyzed using the same methods as for the primary analysis. All other endpoints were summarized descriptively.

RESULTS:

Subject Disposition and Demography: At the time of study termination (18 May 2012), 41 subjects were randomized and 39 subjects were treated with at least 1 dose of study drug. In the anidulafungin treatment group, 26 (100.0%), 24 (92.3%), and 18 (69.2%) of 26 subjects were in the safety, mITT, and PP populations, respectively. In the caspofungin treatment group, 13 (100.0%), 13 (100.0%), and 12 (92.3%) of 13 subjects were in the safety, mITT, and PP populations, respectively. Of the 26 subjects treated in the anidulafungin treatment group, 17 subjects completed the study and 9 subjects discontinued the study, of which 7 subjects discontinued the study due to death. All subjects in the anidulafungin treatment group were analyzed for safety. Of the 13 subjects treated in the caspofungin treatment group, 9 subjects completed the study and 4 subjects discontinued the study due to

death. All subjects in the caspofungin treatment group were analyzed for safety (Table 2). Two subjects were assigned to treatment with anidulafungin, but were not treated.

Table 2. Subject Disposition

No. of Subjects	Anidulafungin	Caspofungin	Total
Screened: N=45			
Assigned to study treatment	28	13	41
Treated	26	13	39
Completed study	17	9	26
Discontinued study	9	4	13
Subject died	7	4	11
Other[a]	1	0	1
Subject no longer willing to participate in study	1	0	1
Analyzed for safety			
Adverse events	26	13	39
Laboratory data	26	13	39

N = number of subjects; No. = number.

a. Withdrawal reason of 'other': Subject admitted to hospital during follow-up period and was unable to return to Investigator site for Follow-Up Visits.

A summary of baseline and demographic characteristics is presented in Table 3 for the safety population. The mean ages of subjects for the anidulafungin and caspofungin treatment groups were 56.3 years and 63.4 years, respectively. The majority of subjects overall were White (33/39 subjects; 84.6%).

Table 3. Demographic and Baseline Characteristics; Safety Population

Parameters	Anidulafungin N=26	Caspofungin N=13
Gender, n		
Male	17	8
Female	9	5
Age (years), n		
18-44	5	2
45-64	13	3
≥65	8	8
Mean	56.3	63.4
SD	16.2	16.3
Range	23–83	26–81
Race, n		
White	21	12
Black	3	1
Other[a]	2	0
Weight (kg)		
Mean	77.3	74.5
SD	27.0	18.3
Range	46.4–142.0	45.0–120.0
APACHE II score by category[b], n (%)		
≤20	23 (88.5)	11 (84.6)
>20	3 (11.5)	2 (15.4)
APACHE II score[b]		
Mean	14.3	15.8
SD	8.84	5.80
Minimum, maximum	2–44	4–27
Median	13.5	16.0

APACHE = Acute Physiology and Chronic Health Evaluation; N = number of subjects; n = number of subjects meeting prespecified criteria; SD = standard deviation.

a. Latin, 1 subject; and East Indian, 1 subject.

b. APACHE II score was available only if performed for clinical reasons; otherwise it was not required by the protocol to be calculated. All subjects in both treatment groups had APACHE II scores available at Baseline.

Twelve subjects discontinued treatment: 7 subjects, and 5 subjects in the anidulafungin and caspofungin treatment groups, respectively. Three subjects discontinued treatment due to death, 1 subject in the anidulafungin treatment group and 2 subjects in the caspofungin treatment group (Table 4).

Table 4. Discontinuations From Treatment; Safety Population

No. of Subjects Discontinued From Treatment	Anidulafungin N=26	Caspofungin N=13
Subject died	1	2
Related to study drug	2	2
Adverse event	1	0
Lack of efficacy	1	2
Not related to study drug	4	1
Global deterioration of health status	1	0
Other[a]	2	1
Subject no longer willing to participate in study	1	0
Total	7	5

N = number of subjects; No. = number

a. Withdrawal reason of 'other': 1 subject (on, caspofungin) discontinued due to medical/familial decision to stop treatment; 1 subject (on, anidulafungin) discontinued due to transfer to long-term care facility; and 1 subject (on, anidulafungin) discontinued due to physician decision to switch subject to fluconazole per hospital policy/standard of care.

Efficacy Results: For the mITT population, the global response (rates of success [primary endpoint]) for anidulafungin and caspofungin at EOT were 20 (83.3%) of 24 subjects and 8 (61.5%) of 13 subjects, respectively. The estimated treatment difference (anidulafungin minus caspofungin) at EOT was 21.8 (95% CI: -12.3, 53.3; Table 5). Results for the PP population supported those for the mITT population.

Table 5. Global Response Rates at End of Treatment (Primary Endpoint); Modified Intent-to-Treat Population

Response	Anidulafungin N=24 n (%)	Caspofungin N=13 n (%)	Difference (95% CI)[a]
Success[b]	20 (83.3)	8 (61.5)	21.8 (-12.3, 53.3)
Failure[c]	2 (8.3)	4 (30.8)	
Indeterminate	1 (4.2)	1 (7.7)	
Missing	1 (4.2)	0	

CI = confidence interval; N = number of subjects; n = number of subjects meeting prespecified criteria.

a. 95% CI is the exact unconditional limits for the difference in global success rate.

b. Global response of success was defined as clinical cure or improvement and microbiologic eradication or presumed eradication.

c. Global response of failure at any time point was carried forward to all subsequent visits.

The global responses (rates of success) at the 2-week and 6-week FU visits were 76.2% and 66.7%, respectively, for the anidulafungin treatment group and 54.5% and 54.5%, respectively, for the caspofungin treatment group (Table 6). According to the clinical protocol, clinical and microbiologic assessments at the 2-week and 6-week FU Visits were not required for subjects who discontinued from treatment for any reason; therefore, only subjects who successfully completed therapy were included in these groups.

Table 6. Global Response Rates (Secondary Efficacy Endpoints); Modified Intent-to-Treat Population

Visit	Response	Anidulafungin n/N (%)	Caspofungin n/N (%)	Difference (95% CI)[a]
Week 2 FU	Success[b]	16/21 (76.2)	6/11 (54.5)	21.6 (-13.6, 55.6)
	Failure[c]	3/21 (14.3)	4/11 (36.4)	
	Indeterminate	1/21 (4.8)	0	
	Missing	1/21 (4.8)	1/11 (9.1)	
Week 6 FU	Success[b]	14/21 (66.7)	6/11 (54.5)	12.1 (-23.3, 47.3)
	Failure[c]	3/21 (14.3)	4/11 (36.4)	
	Indeterminate	0	0	
	Missing	4/21 (19.0)	1/11 (9.1)	

Only subjects who completed treatment and subjects with global response of failure at EOT were included in the 2-week and 6-week FU group.
CI = confidence interval; EOT = end of treatment; FU = follow-up; N = total number of subjects; n = number of subjects meeting prespecified criteria.
a. 95% CI is the exact unconditional limits for the difference.
b. Global response of success was defined as clinical cure or improvement and microbiologic eradication or presumed eradication.
c. Global response of failure at any time point was carried forward to all subsequent visits.

Response (Investigator's assessment) based on clinical cure and microbiologic success (eradication or presumed eradication) at EOT and at the 2-week and 6-week FU Visits in the mITT population is presented in Table 7. Among subjects with clinical cure or improvement and microbiologic eradication or presumed eradication at EOT, 17 (81.0%) of 21 subjects in the anidulafungin treatment group and 5 (62.5%) of 8 subjects in the caspofungin treatment group were reported as having a clinical cure and microbiologic success.

Table 7. Summary of Response (Clinical Cure and Microbiologic Success) by Visit; Modified Intent-to-Treat Population

Response Category	Anidulafungin N=24	Caspofungin N=13
Summary of response at EOT		
Total[a]	21	8
Clinical cure and microbiologic success[b], n (%)	17 (81.0)	5 (62.5)
Summary of response at 2-week follow-up[c]		
Total[a]	16	6
Clinical cure and microbiologic success[b], n (%)	14 (87.5)	6 (100.0)
Summary of response at 6-week follow-up[d]		
Total[a]	15	6
Clinical cure and microbiologic success[b], n (%)	14 (93.3)	6 (100.0)

EOT = end of treatment; N = number of subjects; n = number of subjects meeting prespecified criteria.
a. Total = subjects with clinical cure or improvement and microbiologic eradication or presumed eradication.
b. Microbiologic success = microbiologic eradication or presumed eradication.
c. 2-week follow-up included only subjects who successfully completed treatment and were alive at the EOT.
d. 6-week follow-up included only subjects who were at alive at the 2-week Follow-Up Visit.

For the mITT population, the clinical responses (clinical cure or improvement) for anidulafungin and caspofungin at Day 10 were 17 (70.8%) of 24 subjects and 10 (76.9%) of

13 subjects, respectively. The estimated treatment difference (anidulafungin minus caspofungin) at Day 10 was -6.1 (95% CI: -39.0, 27.9; Table 8).

Table 8. Clinical Response at Day 10; Modified Intent-to-Treat Population

Parameter	Anidulafungin N=24 n (%)	Caspofungin N=13 n (%)
Clinical response		
No. of successes[a]	17 (70.8)	10 (76.9)
No. of failures	0	0
No. of indeterminates	4 (16.7)	2 (15.4)
No. of missing[b]	3 (12.5)	1 (7.7)
Analysis		
Success rate (%)	70.8	76.9
95% CI for treatment groups[c]	(48.9, 87.4)	(46.2, 95.0)
Estimated treatment difference (%)	-6.1	
95% CI for the difference[d]	(-39.0, 27.9)	

CI = confidence interval; N = number of subjects; n = number of subjects meeting prespecified criteria.
a. Successful response was defined as clinical cure or improvement.
b. Missing denoted that the subject had died or the visit was not performed.
c. 95% CI for individual treatment groups was calculated by using the methods of Clopper and Pearson.
d. 95% CI is the exact unconditional limits for the difference.

There were no reported relapses (ie, microbiologic response of recurrence) at the 2-week or 6-week FU Visit for subjects in the mITT population for either treatment group.

There were no reported new infections (ie, microbiologic response of new infection) with an organism not identified at Baseline at the 2-week or 6-week FU Visit for subjects in the mITT population for either treatment group.

A summary of time to first negative blood culture for subjects who had a positive blood culture for *Candida* species on Day 1 of treatment (mITT population) is presented in Table 9. Of the 3 subjects in the anidulafungin treatment group who achieved a negative blood culture (defined as the first of consecutive negative blood cultures separated by at least 24 hours), the median time was 2.0 days (range: 2 to 7 days); of the 4 subjects in the caspofungin treatment group who achieved a negative blood culture, the median time was 3.5 days (range: 2 to 10 days).

Table 9. Summary of Time to First Negative Blood Culture; Modified Intent-to-Treat Population

	Anidulafungin N=3	Caspofungin N=4
No. of subjects with negative blood cultures	3	4
Median (days)	2.0	3.5
Range (days)	2-7	2-10

Analysis included subjects with a positive blood culture for *Candida* species on Day 1 of study treatment. Negative blood culture was defined as the first of consecutive negative blood cultures separated by at least 24 hours.
N = number of subjects; No. = number.

A summary of all-cause mortality for the safety population is presented in Table 10. Of the 7 subject deaths in the anidulafungin treatment group, 1 death was reported at the EOT, 4 deaths were reported at the 2-week FU Visit, and 2 deaths were reported at the 6-week FU Visit. Of the 4 subject deaths in the caspofungin treatment group, 2 deaths each were reported at the EOT and the 2-week FU Visit.

Table 10. Summary of All-Cause Mortality; Safety Population

Total No. of Deaths	Anidulafungin N=26 n (%)	Caspofungin N=13 n (%)
Total No. of deaths	7 (26.9)	4 (30.8)
No. of deaths at EOT	1 (3.8)	2 (15.4)
No. of deaths at 2-week FU	4 (15.4)	2 (15.4)
No. of deaths at 6-week FU	2 (7.7)	0

Table does not include 1 subject who died after participation in the study.
EOT = end of treatment, FU = follow-up; N = number of subjects; n = number of subjects meeting prespecified criteria; No. = number.

Table 11 summarizes time to death for the safety population. Seven (7) of 26 subjects in the anidulafungin treatment group died during the study; the median time to death was 23.0 days (range: 6 to 67 days). Four (4) of 13 subjects in the caspofungin treatment group died during the study, the median time to death was 11.5 days (range: 9 to 51 days).

Table 11. Summary of Time to Death; Safety Population

	Anidulafungin N=26	Caspofungin N=13
Number died (n)	7	4
Median (days)	23.0	11.5
Range (days)	6-67	9-51

Table does not include 1 subject who died after participation in the study.
N = number of subjects; n = number of subjects meeting prespecified criteria.

Safety Results:

Treatment-emergent adverse events (TEAEs) were reported by 24 of 26 subjects in the anidulafungin treatment group and 12 of 13 subjects in the caspofungin treatment group. Of the 135 all-causality TEAEs in the anidulafungin treatment group, 58, 49, and 28 were mild, moderate, and severe, respectively, in severity; 10 of the TEAEs were considered treatment related. Of the 129 all-causality TEAEs in the caspofungin treatment group, 38, 61, and 30 were mild, moderate, and severe, respectively, in severity; none of the TEAEs were considered treatment related. Nineteen (19) subjects overall experienced at least 1 or more treatment-emergent serious adverse event (SAE) during the study, with 1 subject experiencing a treatment-related SAE. The number of TEAEs, SAEs, discontinuations, dose reductions, and temporary discontinuations dues to TEAEs in each treatment group is shown in Table 12.

Table 12. Treatment-Emergent All-Causality and Treatment-Related Adverse Events; Safety Population

No. of Subjects	Anidulafungin N=26		Caspofungin N=13	
	All Causality	Treatment Related	All Causality	Treatment Related
Subjects evaluable for AEs	26	26	13	13
No. of AEs	135	10	129	0
Subjects with AEs	24	7	12	0
Subjects with SAEs	12	1	7	0
Subjects with severe AEs	13	1	9	0
Subjects discontinued due to AEs	1	1	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	0	0	0	0

Included data up to 30 days after last dose of study drug. Except for the number of AEs, subjects were counted only once per treatment in each row. SAEs were according to the Investigator's assessment. SAEs and AEs are not separated out.
AEs = adverse events; N = total number of subjects; No. = number; SAEs = serious adverse event.

Treatment-emergent nonserious AEs (all causality and treatment related) according to Medical Dictionary for Regulatory Activities (MedDRA) (version 15.1) system organ class (SOC) and preferred term (PT) by treatment group are displayed in Table 13.

Table 13. Treatment Emergent Nonserious Adverse Events Reported by ≥5% of Subjects; Safety Population

System Organ Class Preferred Term	Anidulafungin n (%)	Caspofungin n (%)
N (%) of Subjects:		
Evaluable for AEs	26	13
With AEs	21 (80.8)	11 (84.6)
Blood and lymphatic system disorders	1 (3.8)	4 (30.8)
Anaemia	1 (3.8)	3 (23.1)
Coagulopathy	0	2 (15.4)
Neutropenia	0	1 (7.7)
Cardiac disorders	3 (11.5)	3 (23.1)
Atrial fibrillation	1 (3.8)	2 (15.4)
Cardiac failure chronic	0	1 (7.7)
Sinus tachycardia	0	1 (7.7)
Tachycardia	2 (7.7)	1 (7.7)
Eye disorders	0	2 (15.4)
Eye disorder	0	1 (7.7)
Eye haemorrhage	0	1 (7.7)
Pupils unequal	0	1 (7.7)
Gastrointestinal disorders	4 (15.4)	5 (38.5)
Constipation	3 (11.5)	1 (7.7)
Diarrhoea	0	2 (15.4)
Ileus paralytic	1 (3.8)	1 (7.7)
Localised intraabdominal fluid collection	0	1 (7.7)
Nausea	1 (3.8)	2 (15.4)
Oesophageal ulcer	1 (3.8)	1 (7.7)
Rectal haemorrhage	0	1 (7.7)
Vomiting	0	3 (23.1)
General disorders and administration site conditions	3 (11.5)	3 (23.1)
Oedema	2 (7.7)	1 (7.7)
Oedema peripheral	0	2 (15.4)
Pyrexia	1 (3.8)	1 (7.7)
Infections and infestations	3 (11.5)	6 (46.2)
Abdominal abscess	0	1 (7.7)
Abdominal wall abscess	0	1 (7.7)
Abscess	0	1 (7.7)
Clostridium colitis	0	1 (7.7)
Cytomegalovirus infection	0	1 (7.7)
Pneumonia	3 (11.5)	2 (15.4)
Urinary tract infection	0	1 (7.7)
Injury, poisoning and procedural complications	1 (3.8)	1 (7.7)
Post procedural haemorrhage	1 (3.8)	1 (7.7)
Investigations	10 (38.5)	5 (38.5)
Activated partial thromboplastin time prolonged	0	1 (7.7)
Alanine aminotransferase increased	0	1 (7.7)
Aspartate aminotransferase increased	1 (3.8)	1 (7.7)
Aspergillus test positive	1 (3.8)	1 (7.7)
Bacterial test positive	2 (7.7)	1 (7.7)
Bacteroides test positive	0	1 (7.7)
Blood alkaline phosphatase increased	3 (11.5)	2 (15.4)
Blood bilirubin increased	0	1 (7.7)
Blood potassium decreased	1 (3.8)	2 (15.4)
Blood triglycerides increased	0	1 (7.7)
C-reactive protein increased	0	1 (7.7)
Citrobacter test positive	0	1 (7.7)
Corynebacterium test positive	0	1 (7.7)
Cytomegalovirus test positive	0	1 (7.7)
Electrocardiogram T wave inversion	0	1 (7.7)
Enterobacter test positive	1 (3.8)	1 (7.7)

Table 13. Treatment Emergent Nonserious Adverse Events Reported by ≥5% of Subjects; Safety Population

System Organ Class Preferred Term	Anidulafungin n (%)	Caspofungin n (%)
Enterococcus test positive	0	2 (15.4)
Escherichia test positive	0	2 (15.4)
Fungal test positive	0	1 (7.7)
Haematocrit decreased	0	1 (7.7)
Haemoglobin decreased	2 (7.7)	1 (7.7)
Klebsiella test positive	0	1 (7.7)
Platelet count increased	0	1 (7.7)
Proteus test positive	0	1 (7.7)
Staphylococcus test positive	1 (3.8)	3 (23.1)
Streptococcus test positive	1 (3.8)	3 (23.1)
Urine output decreased	0	1 (7.7)
Weight decreased	2 (7.7)	0
Metabolism and nutrition disorders	3 (11.5)	3 (23.1)
Hyperkalaemia	0	1 (7.7)
Hypernatraemia	0	1 (7.7)
Hypoglycaemia	0	1 (7.7)
Hypokalaemia	1 (3.8)	1 (7.7)
Hyponatraemia	0	1 (7.7)
Metabolic acidosis	1 (3.8)	1 (7.7)
Metabolic alkalosis	1 (3.8)	1 (7.7)
Musculoskeletal and connective tissue disorders	0	2 (15.4)
Groin pain	0	1 (7.7)
Muscle haemorrhage	0	1 (7.7)
Nervous system disorders	2 (7.7)	0
Headache	2 (7.7)	0
Psychiatric disorders	4 (15.4)	7 (53.8)
Anxiety	1 (3.8)	1 (7.7)
Catatonia	0	1 (7.7)
Confusional state	1 (3.8)	1 (7.7)
Delirium	1 (3.8)	1 (7.7)
Depression	2 (7.7)	1 (7.7)
Insomnia	0	2 (15.4)
Sleep disorder	1 (3.8)	1 (7.7)
Renal and urinary disorders	0	1 (7.7)
Urinoma	0	1 (7.7)
Respiratory, thoracic and mediastinal disorders	4 (15.4)	7 (53.8)
Chronic obstructive pulmonary disease	0	1 (7.7)
Dyspnoea	1 (3.8)	1 (7.7)
Hyperventilation	0	1 (7.7)
Laryngeal oedema	0	1 (7.7)
Pleural effusion	1 (3.8)	4 (30.8)
Pulmonary embolism	0	1 (7.7)
Respiratory alkalosis	0	2 (15.4)
Respiratory failure	2 (7.7)	1 (7.7)
Tachypnoea	0	1 (7.7)
Wheezing	1 (3.8)	1 (7.7)
Skin and subcutaneous tissue disorders	0	3 (23.1)
Rash	0	2 (15.4)
Skin necrosis	0	1 (7.7)
Vascular disorders	9 (34.6)	4 (30.8)
Deep vein thrombosis	0	1 (7.7)
Haemodynamic instability	0	1 (7.7)
Hypertension	4 (15.4)	2 (15.4)
Hypotension	3 (11.5)	3 (23.1)
Phlebitis	2 (7.7)	2 (15.4)
Shock	1 (3.8)	1 (7.7)

Table 13. Treatment Emergent Nonserious Adverse Events Reported by ≥5% of Subjects; Safety Population

System Organ Class Preferred Term	Anidulafungin n (%)	Caspofungin n (%)

Subjects are only counted once per treatment for each row. Includes data up to 30 days after last dose of study drug.
MedDRA (version 15.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects meeting prespecified criteria; No. = number.

A summary of serious adverse events (SAEs) by treatment group according to MedDRA (version 15.1) SOC and PT by treatment group are displayed in Table 14. One SAE (hypotension) was considered by the Investigator as related to treatment with anidulafungin, captopril, and metoprolol. Of the 7 subjects in the anidulafungin treatment group and 5 subjects in the caspofungin treatment group with SAEs with a fatal outcome, none of the events were considered by the Investigator as related to study treatment.

Table 14. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities); Safety Population

System Organ Class[a] Preferred Term[a]	Anidulafungin n (%)	Caspofungin n (%)
No. (%) of subjects Evaluable for SAEs	26	13
With SAEs	12 (46.2)	7 (53.8)
Blood and lymphatic system disorders	1 (3.8)	0
Haemorrhagic anemia	1 (3.8)	0
Cardiac disorders	0	3 (23.1)
Bradycardia	0	1 (7.7)
Cardiac arrest	0	2 (15.4)
Gastrointestinal disorders	5 (19.2)	0
Abdominal pain	2 (7.7)	0
Duodenal ulcer	1 (3.8)	0
Gastrointestinal haemorrhage	1 (3.8)	0
Intestinal fistula	1 (3.8)	0
Intra-abdominal haemorrhage	1 (3.8)	0
General disorders and administration site conditions	3 (11.5)	0
General physical health deterioration	1 (3.8)	0
Injury associated with device	1 (3.8)	0
Multi organ failure	1 (3.8)	0
Infections and infestations	6 (23.1)	2 (15.4)
Abdominal infection	1 (3.8)	0
Abdominal sepsis	0	1 (7.7)
Infectious peritonitis	1 (3.8)	0
Infectious pleural effusion	1 (3.8)	0
Nosocomial infection	1 (3.8)	0
Peptostreptococcus infection	1 (3.8)	0
Peritonitis	0	1 (7.7)
Septic shock	1 (3.8)	0
Tracheobronchitis	1 (3.8)	0
Injury, poisoning and procedural complication	0	1 (7.7)
Splenic haematoma	0	1 (7.7)
Metabolism and nutrition disorders	0	1 (7.7)
Hypoglycemia	0	1 (7.7)
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	1 (3.8)	0
Acute leukaemia	1 (3.8)	0
Nervous system disorders	0	1 (7.7)
Hypoxic-ischemic encephalopathy	0	1 (7.7)
Renal and urinary disorders	0	1 (7.7)
Renal failure acute	0	1 (7.7)
Respiratory, thoracic, and mediastinal disorders	0	1 (7.7)
Pulmonary embolism	0	1 (7.7)
Skin and subcutaneous tissue disorders	0	1 (7.7)
Pemphigoid	0	1 (7.7)
Vascular disorders	1 (3.8)	1 (7.7)
Hypotension	1 (3.8)	0
Total preferred term events[b]	18	13

Subjects are only counted once per treatment for each row. Includes data up to 30 days after last dose of study drug.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects meeting prespecified criteria;
No. = number; SAE = serious adverse event.
a. MedDRA (version 15.1) coding dictionary applied.
b. Total number of events per subject per treatment group.

One subject was discontinued from the study due to an SAE (hypotension), which was considered by the Investigator to be related to anidulafungin, captopril, and metoprolol Table 15.

Table 15. Discontinuations due to Adverse Events; Safety Population

System Organ Class[a]	Preferred Term[a]	Treatment Phase	Treatment at Onset	Adverse Event			Severity/ Outcome	Causality
				Study Start Day[b]/ Study Stop Day[b]	Time Postdose (Hours)	Duration (Hours)		
Vascular disorders	Hypotension[c]	Active	Anidulafungin	3/4	2.6	10.0	Severe / resolved	Study drug

MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event

a. MedDRA (version 15.1) coding dictionary applied.

b. Day relative to start of study treatment; first day of study treatment = Day 1.

c. SAE according to Investigator's assessment.

Table 16 presents information regarding deaths reported in this study (safety and mITT populations). Eleven (11) of the 12 deaths were unrelated to the infection under study (safety population), of which 8 subjects had no evidence of infection at the time of death (4 subjects in the anidulafungin treatment group, 4 subjects in the caspofungin treatment group).

Table 16. Deaths; Safety and Modified Intent-to-Treat Populations

Treatment Group	Date of First Dose	Date of Last Dose	Date of Death	Day of Death[a]	Cause of Death
Anidulafungin	22 Aug 2011	04 Sep 2011	27 Sep 2011	37	Unknown
	16 Jul 2009	03 Aug 2009	16 Aug 2009	32	Death unrelated to infection under study, but infection was still current
	25 Dec 2010	15 Jan 2011	16 Jan 2011	23	Death unrelated to infection under study, but infection was still current
	29 Apr 2011	22 May 2011	04 Jul 2011	67	Death unrelated to infection under study and no evidence of infection at death
	03 Nov 2009	19 Nov 2009	21 Nov 2009	19	Death unrelated to infection under study and no evidence of infection at death
	23 Apr 2010	25 Apr 2010	28 Apr 2010	6	Death unrelated to infection under study and no evidence of infection at death
	26 Jan 2011	13 Feb 2011	15 Feb 2011	21	Death unrelated to infection under study and no evidence of infection at death
Caspofungin	29 May 2009	07 Jun 2009	08 Jun 2009	11	Death unrelated to infection under study and no evidence of infection at death
	17 Jan 2011	27 Jan 2011	28 Jan 2011	12	Death unrelated to infection under study and no evidence of infection at death
	20 Dec 2009	27 Dec 2009	28 Dec 2009	9	Death unrelated to infection under study and no evidence of infection at death
	04 Mar 2011	14 Apr 2011	23 Apr 2011	51	Death unrelated to infection under study, but infection was still current
	09 Jan 2012	07 Feb 2012	09 Apr 2012	92	Death unrelated to infection under study and no evidence of infection at death

All subjects in this table were in the safety population; specific subjects met the criteria for the mITT population.
One subject died after the end of study participation.
mITT = modified intent-to-treat.
a. Day relative to start of treatment; first day of study treatment = Day 1.

CONCLUSIONS: The results of this descriptive study suggest that anidulafungin was effective for the treatment of deep tissue infection due to *Candida* species with a success rate at the EOT (primary endpoint) of 83.3%.

Although there were numerical differences in the rate of successful global response across the 2 treatment groups, a meaningful interpretation and comparison of treatment outcomes with caspofungin is limited since, by design, the study was not powered to determine statistical significance.

In this study, both anidulafungin and caspofungin were safe and well tolerated. Anidulafungin exhibited a safety profile similar to that observed in the anidulafungin registrational study and approved product labeling.