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PROPRIETARY DRUG NAME/GENERIC DRUG NAME: ERAXIS™/Anidulafungin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See United States Package Insert (USPI)

NATIONAL CLINICAL TRIAL NO.: NCT00689338

PROTOCOL NO.: A8851019

PROTOCOL TITLE: Open-label, Non-Comparative, Study of Intravenous Anidulafungin, Followed Optionally by Oral Voriconazole or Fluconazole Therapy, for Treatment of Documented Candidemia/Invasive Candidiasis in Intensive Care Unit Patient Populations

Study Center(s): 1 center in Austria, 6 centers in Belgium, 3 centers in Canada, 3 centers in Czech Republic, 2 centers in Denmark, 8 centers in France, 3 centers in Germany, 2 centers in Greece, 2 centers in Hungary, 6 centers in Italy, 2 centers in Netherlands, 1 center in Poland, 4 centers in Portugal, 2 centers in Romania, 4 centers in Russian Federation, 2 centers in Slovakia, 4 centers in Turkey, 2 centers in Ukraine and 3 centers in United Kingdom.

Study Initiation and Completion Dates: 19 July 2008 to 27 May 2010

Phase of Development: Phase 3b

Study Objectives:

The primary objectives, as stated in the protocol, were as follows:

- To assess the efficacy of anidulafungin for the treatment of documented candidemia and invasive candidiasis in the following adult specific intensive care unit (ICU) populations with 1 or more of the following covariates:
    - Post-abdominal surgery.
    - Elderly >65 years old (subsequently refined to ≥65 years old).
    - Renal insufficiency/failure/dialysis.
    - Solid tumor.
    - Solid-organ (liver, kidney, lung, heart, pancreas) transplant recipients.

- Hepatic insufficiency.

- Neutropenic (neutrophil count <500/mm^3) including hematology oncology patients.

The primary efficacy endpoint was the global (clinical and microbiological) response at the end of all treatment (EOT). The protocol stated that the global response was to have been assessed by the investigator based on a combination of clinical and microbiological responses. However, in a subsequent change from the protocol, global response was derived using sponsor assessments of clinical and microbiological response.

In a further change from the protocol, for analysis purposes the elderly population was extended to include subjects aged 65 years.

The secondary objectives, as stated in the protocol, were as follows:

- To assess the global treatment response at the end of intravenous (IV) treatment (EOIVT) with anidulafungin.

- To assess global response at 2 weeks after EOT (for subjects who had not switched to a non-study treatment only).

- To assess global response at 6 weeks after EOT (for subjects who had not switched to a non-study treatment only).

- To assess the safety and tolerability of anidulafungin in these adult specific ICU populations.

- To measure the time to first negative blood/tissue culture.

- To evaluate the Day 90 survival (Day 1 being defined as the first day of therapy with anidulafungin).

- To measure the time to ICU discharge.

Additional data were collected in these adult specific ICU populations:

- To test the colonization index = Number of positive sites / Number of tested sites at study entry or at the time when first blood sample was withdrawn for blood culture and at the EOT to further evaluate if there was any correlation (optional).

The exact identification of the sampled sites was collected in the case report form (CRF).

The exact number of tested sites was collected in the CRF.

- To evaluate the *Candida* score at study entry or at the time when first blood sample was withdrawn for blood culture and at the EOT to further evaluate if there was any correlation.

- To evaluate the correlation between candiduria and positive blood/tissue culture.
- To identify the *Candida* species and their frequency in these ICU specific populations.
- To identify the risk factors for candidemia: broad-spectrum antimicrobial agents, cancer chemotherapy, mucosal colonization by *Candida* species, indwelling vascular catheter (especially central venous catheter), total parenteral nutrition (TPN), neutropenia, prior surgery (especially gastrointestinal), and renal failure or hemodialysis, daily oral corticosteroids, immunosuppressive therapy, human immunodeficiency virus infection.
- To describe the primary diagnosis leading to admission into the study.
- Sequential Organ Failure Assessment (SOFA) score.
- Acute Physiology and Chronic Health Evaluation (APACHE) II Score
- Use of mechanical ventilation.
- To assess the plasma pharmacokinetics (PK) of anidulafungin through intense PK sampling in a subset of approximately 25 subjects of a specific ICU subset population.
- To assess the plasma PK of anidulafungin through sparse PK sampling, and to explore the PK/pharmacodynamic relationship of anidulafungin in a subset of no more than 75 subjects of a specific ICU subset population.
- To assess the anidulafungin tissue levels in selected subjects where feasible.

For the secondary objectives of assessment of global response at 2 and 6 weeks after EOT, the caveat 'for subjects who had not switched to a non-study treatment only' that appears in the protocol was erroneous; subjects who had switched to a non-study treatment were also considered.

METHODS

Study Design: This was a Phase 3b, exploratory, prospective, open-label, non-comparative, multicenter, pan-European and Canada study in the ICU setting.

Subjects were to be treated for a minimum of 10 days with IV anidulafungin. On Day 1 subjects were to be treated with a 200 mg loading dose, followed by a 100 mg daily dose from Day 2.

Subjects who completed a minimum of 10 days of IV treatment with anidulafungin could have been switched to oral voriconazole or fluconazole on any day after Day 10, provided that criteria were met to confirm resolution of acute fungal infection. Such subjects were to have continued treatment for a minimum of 14 days after the last positive blood/tissue culture and resolution of signs and symptoms, up to maximum of 56 days from Day 1 of study treatment.

Subjects who were unable to take oral medication were to continue treatment with IV anidulafungin for a minimum of 14 days after the last positive blood/tissue culture and resolution/significant improvement of signs and symptoms of fungal infection, and up to a maximum of 42 days. All subjects meeting the entry criteria, including treatment failures, were expected to return for follow-up visits at Week 2 and Week 6 after the EOT. A follow-up phone call was scheduled to be made on Day 90 to assess survival.

Number of Subjects (Planned and Analyzed): A total enrollment of approximately 286 subjects was planned to yield approximately 200 evaluable subjects in the ICU populations of interest; 216 subjects received treatment and were analyzed.

Diagnosis and Main Criteria for Inclusion: ICU patients with a diagnosis of documented candidemia or invasive candidiasis and belonging to 1 or more of the specific populations detailed in the primary objective.

Study Treatment: Subjects were treated with IV anidulafungin 200 mg IV loading dose on Day 1, followed by 100 mg daily IV dose from Day 2. Subjects who completed a minimum of 10 days of IV treatment with anidulafungin could have been switched to oral voriconazole or fluconazole on any day after Day 10, provided that all criteria were met to confirm the resolution of acute fungal infection.

Efficacy Evaluations: Efficacy evaluations included global response of success, defined as cure or improvement on the clinical response in conjunction with eradication or presumed eradication on the microbiological response, blood/tissue cultures to confirm the presence of *Candida* species as the infecting organism, survival assessment (Day 90), APACHE II, SOFA and *Candida* scores, colonization index, clinical signs and symptoms of fungal infection, time to ICU discharge, and risk factors for candidemia/invasive candidiasis.

Pharmacokinetic Evaluations: PK assessment was optional and was only to be performed at sites which were capable of such PK sampling and in subjects who were determined, in the opinion of the investigator, to be suitable. PK assessments in the study comprised of 3 elements: intensive PK sampling (plasma), sparse PK sampling (plasma), and tissue sampling, each done in a subset of subjects.

Anidulafungin PK parameters were calculated for each subject in the intensive PK sampling group using noncompartmental analysis (Table 1).

Table 1. Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
C_{max}	Maximum observed concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{tau}	Area under the plasma concentration-time profile from time zero to time tau, the dosing interval (24 hours)	Linear/Log trapezoidal method
$t_{½}$ [a]	Terminal elimination half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
CL	Clearance	Dose / AUC_{tau}
V_{ss} [a]	Steady-state volume of distribution	CL * MRT_{inf}, where MRT_{inf} is the mean residence time extrapolated to infinity.

Pharmacokinetic parameter values were calculated using eNCA version 2.2.2.
[a] If data permitted.

Safety Evaluations: Safety evaluations included adverse events (AEs), clinical laboratory evaluations, vital signs, and physical examination.

Statistical Methods: The primary efficacy endpoint was the global treatment response at EOT. The primary endpoint was summarized using both the number and proportion of successes/responses. An exact two-sided 95% confidence interval (CI) was provided for each proportion. Each proportion, and corresponding CI, was expressed as a percentage for presentation purposes. In the primary analysis, any missing values or unknowns were excluded from the calculation of the proportion. In addition, a sensitivity analysis was performed in which any missing or unknown global response at EOT was treated as a failure.

The secondary endpoints of global treatment response at EOIVT and 2 and 6 weeks after EOT, and sponsor assessment of clinical and microbiological treatment response at EOIVT, EOT, and 2 and 6 weeks after EOT were analyzed as for the primary endpoint.

Binary endpoints were analyzed in the same fashion as the primary endpoint.

Time to event endpoints were analyzed using survival methodology. Where the endpoint was survival, a survivor function was estimated using the Kaplan-Meier method. The Kaplan-Meier method was also used to estimate the time to first negative blood culture, time to negativity and time to successful ICU discharge.

Continuous endpoints were summarized using the summary statistics of mean, standard deviation, median, range, number of subjects in the analysis set used and number of subjects with a non missing value of that endpoint at the given visit. A 95% CI was provided for each mean.

Categorical endpoints were summarized by both the number and percentage of subjects in each category, as well as the total number of subjects included in the calculation. Fisher's Exact test was used to assess the association between the 2 categorical variables.

For the intensive PK assessment, concentrations (by nominal time postdose) and PK parameters were summarized descriptively for all subjects. Mean and individual subject concentration-time data were plotted by nominal time postdose. For tissue PK assessments, anidulafungin concentrations in tissue samples and in plasma samples, obtained immediately following excision of the tissue sample, were listed by subject, day, and actual time postdose, and the individual liver-to-plasma ratios were described. The sparse PK samples collected from this study will be pooled with other studies for meta-analysis. Results of the population PK analysis on the integrated data will be reported separately.

Standard analyses of safety data were performed. Additional AE summary tables were produced for elderly subjects (aged ≥65 years). Infusion-related AEs were subdivided based on whether or not subjects had taken anesthetic on the day of the start of the AE.

RESULTS

Subject Disposition and Demography: A total of 221 subjects were screened, and 216 subjects received treatment. Of the treated subjects, 73 subjects (33.8%) completed the study and 143 subjects (66.2%) discontinued. A total of 65 subjects (30.1%) died, 13 subjects (6.0%) discontinued for reasons related to study drug, most commonly lack of efficacy (6 subjects, 2.8%) or AEs (5 subjects, 2.3%), and 65 subjects (30.1%) discontinued for reasons not related to study drug, most commonly because they did not meet the entrance criteria (27 subjects, 12.5%), had a protocol violation (15 subjects, 6.9%), or had an AE (8 subjects, 3.7%).

Of the total 216 subjects, 131 (60.6%) were male and 85 (39.4%) were female. Mean (standard deviation [SD]) age was 61.8 years (14.1 years), with most subjects (189 subjects, 87.5%) aged ≥45 years. Most subjects (199 subjects, 92.1%) were white. Mean (SD) body weight and body mass index were 73.8 kg (19.1 kg) and 25.7 kg/m^2 (6.4 kg/m^2), respectively.

The most common ICU population amongst modified intent-to treat (MITT) subjects (comprising subjects who received at least 1 dose of study drug and who had a positive culture for *Candida* species from a normally sterile site between 96 hours prior to study entry and 48 hours after commencing treatment) was post abdominal surgery (90 subjects, 52.9%). The next most prevalent populations were elderly, specifically ≥65 years old (47.1%), renal insufficiency/failure/dialysis (39.4%), solid tumor (26.5%), and hepatic insufficiency (15.9%). Less than 10% of MITT subjects were either neutropenic (including hematology-oncology) or a solid organ transplant recipient.

Efficacy Results: There were 107/154 subjects (69.5%) who were a global success at EOT in the primary analysis, with associated 95% CI (61.6%, 76.6%) (Table 2). For the sensitivity analysis of global success at EOT, there were 107/170 subjects (62.9%) who were a global success, with associated 95% CI (55.2%, 70.2%).

Table 2. Global Treatment Response at EOT (MITT Population)

	Number (%) of Subjects	Exact 95% Confidence Interval
Primary Analysis[a]		
Success	107 (69.5)	(61.6, 76.6)
Failure	47 (30.5)	
Subjects in Analysis	154	
Sensitivity Analysis[b]		
Success	107 (62.9)	(55.2, 70.2)
Failure	47 (27.6)	
Unknown	12 (7.1)	
Missing	4 (2.4)	
Subjects in Analysis	170	

EOT = end of treatment; MITT = modified intent-to-treat
[a] The primary analysis excluded missing/unknown responses from the percentages.
[b] The sensitivity analysis included missing/unknown responses in the percentages and hence included all subjects in the MITT Population.

Global treatment success rate was 70.7% at EOIVT (95% CI: 62.9%, 77.7%), 60.2% (95% CI: 51.1%, 68.7%) at the 2-week follow-up visit, and 50.5% (95% CI: 40.7%, 60.2%) at the 6-week follow-up visit.

For sponsor assessment of clinical and microbiological response at EOT, success rates were 78.5% (95% CI: 71.1%, 84.8%) and 72.8% (95% CI: 65.1%, 79.6%), respectively.

Mean (SD) time to first negative blood culture was 3.7 (3.07) days, range 2-17 days (including Day 1). Mean (SD) time to negativity was 4.3 (4.86) days, range 2-30 days (again, including Day 1). By Day 2, more than half of subjects in the analysis achieved negativity.

In the MITT population, 78 subjects died on or before Day 90, corresponding to a crude survival rate of 54.1% (95% CI: 46.3%, 61.8%). The Kaplan-Meier estimate of survival at Day 90 was calculated to be 53.8% (95% CI: 45.9%, 60.9%). Mean (SD) time from start of study drug to death was 27.0 days (21.5 days) for the 78 subjects known to have died by Day 90, with time for individual subjects ranging from 1 to 84 days.

Of the 161 subjects included in the analysis, 49 subjects had a successful ICU discharge. Mean (SD) time to successful discharge was 16.2 (9.95) days, range 2-47 days.

Of the 170 subjects in the MITT population, 165 (97.1%) had confirmed *Candida* diagnosis within 96 hours prior to Day 1, and 5 subjects (2.9%) had presumptive diagnosis later confirmed up to 48 hours after Day 1.

In 114 subjects (67.1%), the baseline *Candida* species was only identified in blood. The baseline species was solely present in another normally sterile site (other than blood) in 49 subjects (28.8%), whilst the remaining 7 MITT subjects (4.1%) presented with a *Candida* infection in both blood and another normally sterile site.

The most common baseline *Candida* species in the MITT population was *C. albicans*, which was the only baseline *Candida* species observed in 95 subjects (55.9%).

The most common risk factors for candidemia/invasive candidiasis at screening (MITT population) were use of broad-spectrum antibiotics (90.0%), use of central venous catheter (87.1%), prior surgery (66.5%), and TPN (58.2%).

At the EOT visit, clinical signs and symptoms were less frequently reported than at screening, being most commonly tachycardia >90 bpm (68/150 subjects, 45.3%), mechanical ventilation (60/154 subjects, 39.0%), increased respiratory rate (44/125 subjects, 35.2%), and white blood cell (WBC) count increased (49/142 subjects, 34.5%).

Pharmacokinetic Results: PK parameters from intensive PK sampling (20 subjects) are summarized in Table 3. The $t_{½}$ values reported in this study should be interpreted with caution, since the 24-hour sampling period is shorter than the reported $t_{½}$ of 25 to 40 hours for anidulafungin in the adult development program.

Table 3. Descriptive Summary of Plasma Anidulafungin Pharmacokinetic Parameters in Subjects Receiving 100 mg IV Daily of Anidulafungin

Parameter (units)	No. of Subjects	Parameter Summary Statistics[a]
AUC_{tau} (µg·hr/mL)	20	84.88 (47)
C_{max} (µg/mL)	20	6.81 (54)
T_{max} (hr)	20	1.75 (1.50 - 4.00)
$t_{½}$ (hr)	10	21.51 (12)
CL (mL/min)	20	19.63 (47)
Vss (L)	10	34.79 (52)

IV = intravenous
Parameters are defined in Table 1.
[a] Geometric mean (geometric % coefficient of variation [%CV]) for all parameters except: median (range) for T_{max}; arithmetic mean (%CV) for $t_{½}$.

Two subjects had anidulafungin concentrations measured in liver tissue samples. In one subject at approximately 1.5 hours postdose, liver and plasma concentrations were similar at 8.75 and 7.25 µg/mL, respectively. In the other subject at 13 hours postdose, liver concentration (37.0 µg/mL) was nearly 14-fold higher than plasma concentration (2.66 µg/mL).

Safety Results: There were no treatment-related deaths. Deaths recorded in the safety database are listed in Table 4.

Table 4. Deaths (Safety Database)

Sex/ Age (years)	Day of Death	Event with Fatal Outcome Preferred Term
Page 1 of 3		
IV Anidulafungin → Oral Azole/100 mg		
M/40	15	Cardiac arrest
M/54	49	Acute myeloid leukemia
M/54	6	Death
M/64	34	Gastrointestinal mucosal disorder
M/65	34	Circulatory collapse
M/61	5	Infection
F/56	7	Multi-organ failure
M/78	33	Neurological decompensation
M/50	26	Cardiac arrest
		Hypoxia
F/76	11	Cerebral ischemia
M/45	33	Hemobilia
M/69	22	Disease progression
F/71	57	Pancreatitis necrotizing
		Peritonitis
F/80	28	Sepsis
F/66	42	Esophageal carcinoma
F/51	7	Pancreatic fistula
		Shock hemorrhagic
F/75	16	Septic shock
M/79	10	Septic shock
F/79	7	Hemodynamic instability
M/81	11	Sepsis
M/42	12	Septic shock
M/78	30	Fecal incontinence
F/77	40	Acute respiratory failure
		Pulmonary edema
F/79	24	Acute respiratory distress syndrome
M/75	11	Renal failure
M/43	8	Respiratory failure
M/75	13	Multi-organ failure
F/81	9	Not applicable
M/68	32	Peritonitis
		Respiratory failure
M/74	22	Multi-organ failure
M/40	47	Urosepsis
M/76	6	Septic shock
M/77	7	Multi-organ failure
M/75	27	Multi-organ failure
M/60	39	Multi-organ failure
M/44	42	Multi-organ failure
		Septic shock
M/70	12	Septic shock
F/65	4	Septic shock
M/77	37	General physical health deterioration
M/72	16	Acute respiratory distress syndrome

M = male; F = female; IV = intravenous

Table 4. Deaths (Safety Database)

Sex/ Age (years)	Day of Death	Event with Fatal Outcome Preferred Term
Page 2 of 3		
F/57	6	Condition aggravated
		Septic shock
M/unknown	Not applicable	Cardiopulmonary failure
M/80	29	Septic shock
M/62	20	Pneumonia
		Septic shock
M/42	10	Shock hemorrhagic
M/64	20	Abdominal abscess
M/51	6	Pneumothorax
M/75	27	Disease progression
		Pancreatic carcinoma
M/50	16	Cardio-respiratory arrest
F/65	19	Cardiac arrest
F/77	8	Multi-organ failure
		Septic shock
F/64	3	Cardiac failure acute
M/72	38	Cardiac failure
F/55	37	Cardiac failure
M/69	7	Gastrointestinal hemorrhage
F/47	52	Pneumonia
		Septic shock
F/69	40	Multi-organ failure
M/63	24	Multi-organ failure
F/70	15	Ileus paralytic
		Sepsis
M/57	8	Cardiac failure
F/84	5	Bacterial sepsis
		Respiratory failure
F/43	5	Cardiac arrest
		Septic shock
F/63	10	Cardiac arrest
		Multi-organ failure
		Septic shock
M/65	5	Cardiac arrest
		Septic shock

M = male; F = female

Table 4. Deaths (Safety Database)

Sex/ Age (years)	Day of Death	Event with Fatal Outcome Preferred Term
Page 3 of 3		
IV Anidulafungin → Oral Azole/200 mg		
M/82	14	Intestinal ischemia
F/71	8	Aortic embolus
		Cellulitis
		Infection
		Renal failure
		Rhabdomyolysis
		Sepsis
M/34	1	Cardiac arrest
F/44	63	Cardio-respiratory arrest
M/69	57	Cardiac disorder
M/55	1	Pulmonary embolism
M/70	2	Sepsis
M/89	3	Disease progression
		Gastric cancer
F/69	212	Not applicable
M/62	2	Septic shock
M/80	46	Respiratory failure
		Sepsis
F/71	3	Multi-organ failure
		Septic shock
F/86	2	Septic shock
F/82	7	Multi-organ failure
M/88	1	Multi-organ failure
		Septic shock
M/61	6	Sepsis
F/78	2	Cardiac arrest
		Septic shock
IV Anidulafungin → Oral Azole/400 mg		
F/66	57	Cardiac arrest
M/43	48	Cardio-respiratory arrest
M/52	30	Disease progression
M/79	24	Pneumonia
M/71	33	Gastrointestinal hemorrhage
M/53	38	Peritonitis

M = male; F = female; IV = intravenous

Less than 2% of subjects experienced a treatment-related serious AE (SAE) according to the study database. Convulsion was the only treatment-related SAE reported for more than 1 subject (Table 5); 1 of these 2 cases was not considered to be related to treatment by the sponsor.

Table 5. Treatment-Related Serious Adverse Events

Sex/ Age (years)	Adverse Event Preferred Term	Start/ Stop Day	Severity	Outcome
M/54	Convulsion	4/[>6]	Moderate	Still present
F/40	Hyperglycemia	34/43	Severe	Resolved
F/59	Convulsion[a]	9/21	Moderate	Resolved
M/25	Tachycardia	1/2	Severe	Resolved
	Chills	1/1	Severe	Resolved
	Infusion-related reaction	1/2	Severe	Resolved
	Body temperature increased	1/1	Severe	Resolved
	Hypotension	1/2	Severe	Resolved
M/37	Bronchospasm	3/3	Moderate	Resolved

M = male; F = female
[a] Was not considered to be related to treatment by the sponsor.
[ ] Values in brackets were imputed from incomplete dates and times.

The most common AEs were diarrhea (10.2%), septic shock (9.7%) and anemia, hypertension, and hypotension (each 7.4%) (Table 6). The most common treatment-related AE was erythema (1.9%). A total of 6 subjects experienced AEs that were considered to potentially be infusion-related.

Table 6. Incidence of Most Common Adverse Events by Preferred Term (Reported for ≥5% of Subjects and/or ≥1% of Subjects if Treatment-Related)

	IV Anidulafungin → Oral Azole (N=216)	
Number (%) of Subjects with Adverse Event	**All Causalities**	**Treatment-Related**
Diarrhea	22 (10.2)	3 (1.4)
Septic shock	21 (9.7)	0
Anemia	16 (7.4)	1 (0.5)
Hypertension	16 (7.4)	2 (0.9)
Hypotension	16 (7.4)	3 (1.4)
Multi-organ failure	13 (6.0)	0
Atrial fibrillation	12 (5.6)	3 (1.4)
Nausea	12 (5.6)	1 (0.5)
Pyrexia	12 (5.6)	2 (0.9)
Tachycardia	12 (5.6)	2 (0.9)
Thrombocytopenia	12 (5.6)	2 (0.9)
Cardiac arrest	11 (5.1)	0
Erythema	6 (2.8)	4 (1.9)
Aspartate aminotransferase increased	3 (1.4)	3 (1.4)
Blood alkaline phosphatase increased	3 (1.4)	3 (1.4)

IV = intravenous; N = number of subjects; MedDRA = Medical Dictionary for Regulatory Activities
If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken.
Subjects were counted only once per treatment in each row. Any missing severities were imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized. Missing baseline severities were imputed as mild.
Includes data up to 30 days after last dose of study drug.
MedDRA (v13.0) coding dictionary applied.

For subjects aged ≥65 years, the most common AEs were hypotension (12.0%), diarrhea (10.0%), and septic shock (10.0%); all other AEs were reported for ≤9.0% of subjects.

Five subjects discontinued due to AEs that were considered to be related to study drug (convulsion, hypernatremia, drug hypersensitivity, bronchospasm, and transaminases increased) (Table 7).

Table 7. Discontinuations Due to Adverse Events

Sex/ Age (years)	Adverse Event Preferred Term	Start/ Stop Day	Severity	Causality	SAE
M/54	Convulsion	4/[>6]	Moderate	Study drug	Yes
M/65	Hypernatremia	6/51	Severe	Study drug	No
M/33	Septic embolus	7/7	Severe	Disease under study	Yes
M/78	Nervous system disorder[a]	31/[>33]	Severe	Disease under study	Yes
F/21	Drug hypersensitivity	7/7	Mild	Study drug	No
M/75	Cardiac failure	9/[>11]	Moderate	Other illness[b]	Yes
F/71	Septic shock	1/3	Severe	Disease under study	Yes
F/46	Infectious disease carrier	16/[>59]	Severe	Disease under study	No
F/65	Septic shock	2/4	Severe	Disease under study	Yes
F/82	Multi-organ failure	1/[>7]	Severe	Disease under study	Yes
M/37	Bronchospasm	3/3	Moderate	Study drug	Yes
F/68	Multi-organ failure	36/[>40]	Severe	Other illness[c]	Yes
M/86	Transaminases increased	11/[>49]	Moderate	Study drug	No

M = male; F = female; SAE = serious adverse event
[a] Investigator entry 'neurological deterioration'
[b] Congestive heart insufficiency
[c] Renal failure, hepatic failure, cardiac failure
[ ] Values in brackets were imputed from incomplete dates and times.

There were no marked changes for clinical laboratory evaluations, blood pressure, heart rate, weight, temperature, or respiration rate. Ten subjects were potential Hy's law cases; nearly all cases reported either a co-morbid medical conditions or significant medical history that could possibly account for the reported abnormal hepatic enzyme values.

CONCLUSIONS:

- There were 107/154 subjects (69.5%) who were a global success at EOT in the primary analysis, with associated 95% CI (61.6%, 76.6%).

- For the sensitivity analysis of global success at EOT, which included an additional 16 subjects with response either unknown or missing, there were 107/170 subjects (62.9%) who were a global success, with associated 95% CI (55.2%, 70.2%).

- For the primary analysis, global treatment success rate was 70.7% at EOIVT (95% CI: 62.9%, 77.7%), 60.2% (95% CI: 51.1%, 68.7%) at the 2-week follow-up visit, and 50.5% (95% CI: 40.7%, 60.2%) at the 6-week follow-up visit.

- For sponsor assessment of clinical response at EOT, success rate was 78.5% (95% CI: 71.1%, 84.8%).

- For sponsor assessment of microbiological response at EOT, success rate was 72.8% (95% CI: 65.1%, 79.6%).

- Of the ICU populations with at least 20 evaluable subjects, global treatment response was lowest for elderly subjects and greatest for subjects with renal

insufficiency/failure/dialysis, although there was considerable overlap of 95% CI between the groups.

- In terms of baseline *Candida* species, success rate in the primary analysis generally ranged from 60.0% to 74.4%; an exception to this was for *C. tropicalis*, where the success rate was only 36.4%. However, there was considerable overlap of 95% CI across these groups.

- Success rate in the primary analysis was similar (approximately 70%) for the group of subjects who had an APACHE II score ≤20 and the group of subjects who had a score >20 at screening.

- Success rate in the primary analysis was greater for subjects who had all intravascular catheters removed/replaced on or before Day 3 (77.1%; 95% CI: 59.9%, 89.6%) compared to those who did not (60.0%; 95% CI: 44.3%, 74.3%), although there was considerable overlap of the 95% CI.

- For subjects who attained a first negative blood culture not followed by positive blood culture in the next 3 days (or 4 days if this negative was observed on or after Day 10) until EOIVT, mean (SD) time to first negative blood culture was 3.7 (3.07) days, range 2-17 days (including Day 1). For subjects who achieved negativity (first negative blood culture not followed by positive blood culture until EOIVT), mean (SD) time to negativity was 4.3 (4.86) days, range 2-30 days (again, including Day 1). By Day 2, more than half of subjects in the analysis achieved negativity.

- In the MITT Population, 78 subjects died on or before Day 90, corresponding to a crude survival rate of 54.1% (95% CI: 46.3%, 61.8%). The Kaplan-Meier estimate of survival at Day 90 was calculated to be 53.8% (95% CI: 45.9%, 60.9%). Mean (SD) time from start of study drug to death was 27.0 days (21.5 days) for the 78 subjects known to have died by Day 90, with time for individual subjects ranging from 1 to 84 days.

- Of the 161 subjects included in the analysis, 49 subjects had a successful ICU discharge. Mean (SD) time to successful discharge was 16.2 (9.95) days, range 2-47 days.

- Of the 170 subjects in the MITT population, 165 (97.1%) had confirmed *Candida* diagnosis within 96 hours prior to Day 1, and 5 subjects (2.9%) had presumptive diagnosis later confirmed up to 48 hours after Day 1.

- In 114 subjects (67.1%), the baseline *Candida* species was only identified in blood. The baseline species was solely present in another normally sterile site (other than blood) in 49 subjects (28.8%), whilst the remaining 7 MITT subjects (4.1%) presented with a *Candida* infection in both blood and another normally sterile site.

- The most common baseline *Candida* species in the MITT population was *C. albicans*, which was the only baseline *Candida* species observed in 95 subjects (55.9%).

- The most common risk factors for candidemia/invasive candidiasis at screening (MITT population) were use of broad-spectrum antibiotics (90.0%), use of central venous catheter (87.1%), prior surgery (66.5%), and TPN (58.2%).

- In the MITT population, 112 subjects (65.9%) only received IV anidulafungin as study drug. The remaining subjects were administered an oral azole following anidulafungin as part of their treatment regimen; 44 subjects (25.9%) received fluconazole and 14 subjects (8.2%) received voriconazole.

- At the EOT visit, clinical signs and symptoms were less frequently reported than at screening, being most commonly tachycardia >90 bpm (68/150 subjects, 45.3%), mechanical ventilation (60/154 subjects, 39.0%), increased respiratory rate (44/125 subjects, 35.2%), and WBC count increased (49/142 subjects, 34.5%).

- The PK profile of anidulafungin in ICU population at 100 mg IV daily was comparable to that in other patient populations at the same dosing regimen.

- There were no treatment-related deaths. Less than 2% of subjects experienced a treatment-related SAE according to the study database.

- The most common AEs were diarrhea (10.2%), septic shock (9.7%) and anemia, hypertension, and hypotension (each 7.4%); all other AEs were reported for ≤6.0% of subjects. No treatment-related AEs were reported for ≥2% of subjects, the most common treatment-related AE being erythema (1.9%).

- A total of 6 subjects experienced AEs that were considered to potentially be infusion-related.

- AEs were reported in the System Organ Class (SOC) Hepatobiliary disorders for 24 subjects (11.1%), most commonly cholestasis (5 subjects, 2.3%). Treatment-related AEs in the SOC Hepatobiliary disorders were reported for 7 subjects (3.2%).

- Two subjects (0.9%) experienced an AE of convulsion. In both cases the event was considered to be a treatment-related SAE by the investigator; 1 of the cases was not deemed to be related to treatment by the sponsor

- For subjects aged ≥65 years, the most common AEs were hypotension (12.0%), diarrhea (10.0%), and septic shock (10.0%); all other AEs were reported for ≤9.0% of subjects. No treatment-related AEs were reported for >2% of subjects aged ≥65 years.

- Five subjects discontinued due to AEs that were considered to be related to study drug (convulsion, hypernatremia, drug hypersensitivity, bronchospasm, and transaminases increased).

- There were no marked changes for clinical laboratory evaluations, blood pressure, heart rate, weight, temperature, or respiration rate. Ten subjects were potential Hy's law cases;

nearly all cases reported either a co-morbid medical conditions or significant medical history that could possibly account for the reported abnormal hepatic enzyme values.