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PROPRIETARY DRUG NAME/INN: Eraxis™/Anidulifungin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT #: 00037206

PROTOCOL NO.: VER002-7

PROTOCOL TITLE: An Open Label Non-Comparative Study of the Safety and Efficacy of Intravenous Anidulafungin Plus AmBisome® [(Amphotericin B) Liposome for Injection] as a Treatment for Invasive Aspergillosis

Study Center(s): Twelve (12) study centers enrolled subjects including 5 centers in the United States, 1 center in the United Kingdom, 2 centers in France, 1 center in Belgium, 1 center in Switzerland and 2 centers in South Africa.

Study Initiation and Completion Dates: 13 May 2002 to 06 February 2003

The study was terminated prematurely.

Phase of Development: Phase 2/3

Study Objective(s):

Primary: To determine the global response (clinical and radiological) of intravenous (IV) anidulafungin plus AmBisome ([amphotericin B] liposome for injection) as a treatment for patients with invasive aspergillosis (IA)

Secondary: To determine the safety of IV anidulafungin plus AmBisome as a treatment for patients with IA, and to characterize the relationship between anidulafungin concentrations and specific indices of safety and efficacy by performing population pharmacokinetic (PK) analysis on plasma samples from patients with IA

METHODS

Study Design:

This was an open-label, non-comparative, multi-center, multinational study of IV anidulafungin plus AmBisome as a treatment for IA conducted in patients with a diagnosis of

definite or probable IA. An independent Data Review Committee (DRC) was constituted in order to confirm the eligibility of each patient and to adjudicate the clinical radiologic, and microbiologic responses at EOT and FU. The DRC also stratified patients into 2 categories based on their underlying disease: stratum A– patients with proven or probable IA following allogeneic bone marrow or stem cell transplantation or those with proven extrapulmonary IA and stratum B– proven or probable pulmonary IA or pulmonary IA with unproved extrapulmonary IA.

All subjects received the combination therapy of IV anidulafungin plus AmBisome. On Day 1, subjects received a 200 mg loading dose of anidulafungin followed by AmBisome at a dose ≤ 5 mg/kg/day. From Day 2 onwards, subjects received a daily 100 mg dose of anidulafungin followed by AmBisome at a dose of ≤ 5 mg/kg/day. Investigators could reduce the dose of AmBisome as necessitated by toxicity of the drug. Assessments were performed daily.

All subjects were to continue combination therapy with IV anidulafungin plus AmBisome until resolution of signs and symptoms of IA, as determined by the Investigator, or for a maximum of 90 days. While it was preferred that treatment with the combination of anidulafungin and AmBisome continue until disease resolution, subjects who did not tolerate AmBisome were allowed to continue treatment with anidulafungin alone. End-of-therapy (EOT) was considered to be the point at which anidulafungin/AmBisome therapy for IA was discontinued. A post-therapy follow-up (FU) evaluation was performed 4 weeks after EOT, or earlier in the event of either relapse or introduction of another systemic antifungal therapy. Efficacy, pharmacokinetic and safety evaluations were performed.

Number of Patients (planned and analyzed):

Planned: Approximately 60 evaluable subjects were planned.

Analyzed: A total of 32 subjects were enrolled. By the interim analysis, 30 subjects received at least 1 dose of study medication. Due to early termination, the total planned number of subjects were not enrolled.

Diagnosis and Main Criteria for Inclusion:

Subjects were males or females, aged ≥ 18 years, who had a diagnosis of definite extrapulmonary IA or definite or probable pulmonary IA. Subjects were excluded if they had received >5 days of therapeutic doses of systemic antifungal therapy with activity against *Aspergillus* for the treatment of the current condition under study or a cumulative dose of more than 5 mg/kg of amphotericin, 25 mg/kg of a lipid formulation of amphotericin, 350 mg caspofungin, 3 g of IV voriconazole, 2 g of oral voriconazole, or 2 g of itraconazole for the treatment of the current condition under study. Prior prophylactic use of azoles or amphotericin was acceptable and did not count towards this exclusion. The prior prophylactic use of caspofungin acetate was not permitted. The exclusion for subjects who received > 5 days of therapy or who exceeded the cumulative dosage of the systemic antifungal therapies specified above did not apply to subjects considered treatment failures.

Study Treatment:

Both anidulafungin (200 mg loading dose/100 mg daily maintenance dose) and AmBisome ($\leq 5\text{mg/kg/day}$) were administered daily by IV infusion at approximately the same time each day using a certified and validated infusion pump. The infusion of anidulafungin was to have been completed at least 1 hour prior to the infusion of AmBisome. Study treatment continued for a maximum of 90 days.

Efficacy Evaluations:

The *primary efficacy variable* was the global response (based on the clinical and radiological responses) at EOT in the modified ITT population.

Pharmacokinetic Evaluations:

Anidulafungin plasma concentrations were determined on up to 4 occasions [Day 3 (0-4 hours following the end of infusion), Day 7 (pre-dose), Day 14 (8-12 hours following the end of infusion), and Day 21 (pre-dose, only if the patient was still receiving anidulafungin)].

Safety Evaluations:

Safety assessments throughout the study included monitoring of AEs, clinical laboratory tests, 12-lead electrocardiogram (ECG) measurements, physical examination findings, vital signs and chest X-ray results (on Day 1, and daily during treatment).

Statistical Methods:

Following completion of 30 patients, a decision was made by the Sponsor not to perform a formal futility analysis but to terminate the study. Therefore, a final analysis of efficacy, safety and pharmacokinetics was performed on data from 30 patients.

Analysis Populations:

Intent-to-Treat (ITT) Population: All subjects who received at least 1 dose of anidulafungin were included in the ITT population.

Modified Intent-to-Treat (Modified ITT) Population: All ITT subjects who were either stratum A (subjects with proven extrapulmonary IA or IA post bone marrow or stem cell transplant) or stratum B (subjects with pulmonary IA not included in stratum A) were included in the modified ITT population.

Microbiological Intent-to-Treat (Microbiological ITT) Population: All modified ITT subjects who had a positive culture at baseline were included in the microbiological ITT population.

Safety Population: All subjects who had been enrolled and had received at least 1 dose of anidulafungin were evaluable for safety. (Note that this population is the same as the ITT population).

Methods:

Efficacy, safety, and anidulafungin concentration data were presented using descriptive statistics for the ITT populations; there were no evaluable populations. Anidulafungin concentrations were analyzed using nonlinear mixed effects modeling and a previously described anidulafungin population PK model.

RESULTS

Subject Disposition and Demography:

Subject disposition and details regarding discontinuation from treatment are summarized in Table S1.

Table S1 Subject Disposition and Reasons for Discontinuation of Treatment

Characteristic	Total N= 30 n (%)
Total Subjects Enrolled	32
Total Subjects Receiving at Least 1 Dose of Anidulafungin	30 (100)
Study Completion Status	
Total Subjects Who Completed the Study Through Follow-up	12 (40.0)
Total Subjects Who Discontinued the Study	18 (60.0)
Primary Reason for Study Discontinuation	
Adverse event	14 (46.7)
At the request of the subject, investigator, or sponsor	1 (3.3)
Insufficient therapeutic effect	3 (10.0)

Most subjects in this study were Caucasian, with a higher proportion of males (73%, n= 22) than females (27%, n= 8). The mean age was 58 years, ranging from 21 to 79 years; 11 (37%) subjects were greater than 65 years of age. A higher percentage of subjects fell under stratum B and the most common diagnosis was pulmonary aspergillosis.

Investigators diagnosed more subjects (73%) with pulmonary aspergillosis compared with the Data Review Committee (DRC [60%]); most cases were probable rather than proven pulmonary IA. Many of the subjects enrolled in this study had risk factors indicating a poor prognosis. Almost one-half of the subjects were neutropenic at baseline, and more than one-half of subjects had cancer as the source of immunosuppression.

For the microbiological ITT population, *A. fumigatus* was the most common pathogen isolated.

Efficacy Results:

An interim analysis of safety was reported on 14 March 2003, with results from 17 subjects. A per-protocol interim analysis of safety and efficacy was planned when 30 subjects completed, at which time the Sponsor closed enrollment. Primary efficacy results from the completed study are shown in Table S2.

Table S2 Global Response at EOT (Modified ITT Population)

Global Response Global Outcome	Stratum A ^b N= 8 n (%)	Stratum B N= 17 n (%)	Total N= 25 n (%)
<i>Per DRC</i>			
Success	3 (38)	4 (24)	7 (28) ^c
Partial response	3 (38)	4 (24)	7 (28)
Failure	5 (63)	13 (76)	18 (72)
Failure	3 (38)	8 (47)	11 (44)
Stable disease	2 (25)	5 (29)	7 (28)
<i>Per Investigator^a</i>			
Success	2 (25)	4 (24)	6 (24) ^d
Success	2 (25)	4 (24)	6 (24)
Failure	6 (75)	13 (76)	19 (76)
Failure	4 (50)	13 (76)	17 (68)
Indeterminate	2 (25)	0 (0.0)	2 (8)

^aDetermined programmatically based on the investigator's clinical and radiologic response.

^bStratum A= Subjects with proven extrapulmonary IA or IA post bone marrow or stem cell transplant); Stratum B= subjects with pulmonary IA not included in stratum A.

^c95% confidence interval around success rate is 12.1% – 49.4%.

^d95% confidence interval around success rate is 9.4% – 45.1%.

DRC= Data Review Committee

Pharmacokinetic Results:

Individual PK data from this study were combined with demographic variables and appended to the data that were used to build a previously described population PK model of anidulafungin pharmacokinetics (Dowell, 2004). Observed versus predicted concentrations were distributed about the line of unity and weighted residuals were evenly distributed across zero.

Safety Results:

Duration of Exposure:

The median and mean duration of anidulafungin therapy was 22 and 27 days, respectively. The median and mean duration of AmBisome therapy was 22 and 26 days, respectively. The range of exposure for anidulafungin was 1 to 90 days. With 1 exception, all patients received combination therapy. A single patient received 170 mg of anidulafungin but no AmBisome because this patient died from a massive pulmonary hemorrhage during the first infusion. The patient's death was considered to be associated with existing disease rather than with study treatment.

Adverse Events:

All 30 subjects reported at least 1 AE during this study; 18 of 30 (60%) experienced AEs that were possibly or probably related to the study drug. Adverse events, by relationship to study drug, are summarized in Table S3.

Table S3 Adverse Events Occurring in 2 or More Subjects by Relationship to Study Drug

Preferred Term	Total N= 30		
	Related (probably or possibly) for anidulafungin n (%)	Possibly, probably related, expected event for AmBisome n (%)	Unrelated n (%)
Subjects with any AE	18 (60.0)	11 (36.7)	30 (100.0)
Blood alkaline phosphatase NOS increased	5 (16.7)	4 (13.3)	4 (13.3)
Hypokalemia	2 (6.7)	2 (6.7)	4 (13.3)
Pyrexia	1 (3.3)	0 (0.0)	5 (16.7)
Liver function tests NOS abnormal	3 (10.0)	1 (3.3)	2 (6.7)
Nausea	2 (6.7)	1 (3.3)	3 (10.0)
Anxiety NEC	1 (3.3)	0 (0.0)	4 (13.3)
Gamma-glutamyltransferase increased	3 (10.0)	2 (6.7)	1 (3.3)
Blood bilirubin increased	2 (6.7)	1 (3.3)	2 (6.7)
Abdominal pain NOS	1 (3.3)	1 (3.3)	3 (10.0)
Headache NOS	1 (3.3)	0 (0.0)	3 (10.0)
Renal impairment NOS	2 (6.7)	2 (6.7)	1 (3.3)
Diarrhea NOS	1 (3.3)	0 (0.0)	2 (6.7)
Hypomagnesemia	1 (3.3)	0 (0.0)	2 (6.7)
Myalgia	1 (3.3)	1 (3.3)	2 (6.7)
Rash NOS	1 (3.3)	0 (0.0)	2 (6.7)
Tachycardia NOS	1 (3.3)	0 (0.0)	2 (6.7)
Weakness	1 (3.3)	0 (0.0)	2 (6.7)
Flushing	2 (6.7)	0 (0.0)	0 (0.0)

AE= Adverse event, NOS= Not otherwise specified, n= Number of subjects with the AE (preferred term), N= Number of total intent-to-treat subjects, NEC= Not elsewhere classified.
 A patient who experienced multiple events was counted once for “Patients With Any AE”.

Serious Adverse Events:

Twenty-three (23) subjects had a total of 33 SAEs; seventeen (17) of these subjects died due to a SAE. Serious adverse events are summarized in Table S4.

Table S4 Serious Adverse Events During Treatment^a (Total N= 30)

Preferred Term	n (%)
Subjects With Any SAE	23 (76.7)
Hemoptysis	2 (6.7)
Liver function tests NOS abnormal	2 (6.7)
Pneumonia NOS	2 (6.7)
Renal failure NOS	2 (6.7)
Respiratory distress	2 (6.7)
Respiratory failure	2 (6.7)
Acute myeloid leukemia NOS	1 (3.3)
Acute respiratory failure	1 (3.3)
Bronchopulmonary aspergillosis	1 (3.3)
Calculus renal NOS	1 (3.3)
Cerebral hemorrhage	1 (3.3)
Chronic myeloid leukemia	1 (3.3)
Chronic obstructive airways disease	1 (3.3)
Cryptogenic organizing pneumonia	1 (3.3)
Endocarditis fungal NOS	1 (3.3)
Gastrointestinal hemorrhage NOS	1 (3.3)
Hypopnea	1 (3.3)
Leukemia NOS	1 (3.3)
Lung infiltration NOS	1 (3.3)
Prolymphocytic leukemia	1 (3.3)
Pulmonary embolism	1 (3.3)
Pyrexia	1 (3.3)
Sepsis NOS	1 (3.3)
Septic shock	1 (3.3)
Vascular pseudoaneurysm	1 (3.3)
Venous thrombosis NOS limb	1 (3.3)
Weakness	1 (3.3)

NOS= Not otherwise specified, n= Number of subjects with AE (preferred term), N= Number of total intent-to-treat subjects, SAE= Serious adverse event.

^aA patient who experienced multiple events was counted once for “Patients With Any AE”.

Discontinuations:

Fourteen (14) subjects had an AE that led to discontinuation of study drug. Adverse events that led to discontinuation of study drug were serious for 13 subjects, 12 of whom had an outcome of death and 1 of whom recovered (and non-serious for 1 patient, although this patient was also withdrawn from the study medication due to the adverse event of confusion). Adverse events leading to discontinuation of study drug are shown in Table S5.

Table S5 Adverse Events Leading to Discontinuation of Study Drug^a

Preferred Term	Anidulafungin discontinued N= 30 n* (%)	AmBisome Discontinued N [†] = 29 n*(%)	Anidulafungin & AmBisome discontinued N [†] = 29 n* (%)	Total N= 30 n (%)
Subjects With Any AE Leading to Discontinuation	1 (3.3)	1 (3.4)	13 (44.8)	14 (46.7)
Respiratory failure (excl neonatal)	0 (0.0)	0 (0.0)	2 (6.9)	2 (6.7)
Bronchopulmonary aspergillosis	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)
Chronic myeloid leukemia	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)
Confusion	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)
Cryptogenic organizing pneumonia	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)
Endocarditis fungal NOS	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)
Gastrointestinal hemorrhage NOS	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)
Hemoptysis	1 (3.3)	0 (0.0)	0 (0.0)	1 (3.3)
Leukemia NOS	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)
Liver function tests NOS abnormal	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)
Pneumonia NOS	0 (0.0)	1 (3.4)	0 (0.0)	1 (3.3)
Prolymphocytic leukemia	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)
Respiratory distress	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)
Sepsis NOS	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.3)

Excl= Excluding, NOS= Not otherwise specified, n= Number of subjects with the AE (preferred term) and discontinuation of the study drug (anidulafungin, AmBisome or both) due to the AE, N= Number of total ITT subjects, n*= Number of subjects with the AE (Preferred Term) and discontinuation of the specified study drug due to the AE, N[†]= Number of ITT subjects who received AmBisome or anidulafungin and AmBisome, respectively.

^aA subject who experienced multiple events was counted once for “Patients With Any Adverse Event Leading to Discontinuation”.

Deaths:

There were 17 deaths in this study. None of the AEs leading to death was related to study medication. Deaths are summarized in Table S6.

Table S6 Adverse Events Leading to Death^a

Preferred Term	Total N= 30 n (%)
No. of Subjects Who Died	17 (56.7)
No. of Events Leading to Death	18
Hemoptysis	2 (6.7)
Respiratory distress	2 (6.7)
Respiratory failure (excl neonatal)	2 (6.7)
Acute respiratory failure	1 (3.3)
Bronchopulmonary aspergillosis	1 (3.3)
Chronic myeloid leukemia	1 (3.3)
Cryptogenic organizing pneumonia	1 (3.3)
Gastrointestinal hemorrhage NOS	1 (3.3)
Hypopnea	1 (3.3)
Leukemia NOS	1 (3.3)
Pneumonia NOS	1 (3.3)
Prolymphocytic leukemia	1 (3.3)
Pulmonary embolism	1 (3.3)
Sepsis NOS	1 (3.3)
Septic shock	1 (3.3)

AE= Adverse event, Excl= Excluding, n= Number of subjects who had the AE (preferred term) leading to death, N= Number of total ITT subjects, NOS= Not otherwise specified.

^aA patient who experienced multiple events was counted once for “Patients With Any AE”.

Clinical Laboratory Data:

Hematology:

Potentially clinically significant (PCS) low hemoglobin and hematocrit values (defined as ≤ 0.8 x lower limit of normal [LLN] for each parameter) were observed for 76.7% and 73.3% of subjects, respectively, at baseline, and for 87.5% and 83.3% of subjects, respectively, at EOT. The proportion of subjects with PCS high white blood cell (WBC) values (defined as ≥ 2.0 x upper limit of normal [ULN]) decreased slightly from 20.0% of subjects at baseline to 12.5% at EOT. The proportions of subjects with PCS low WBC values (defined as ≤ 0.5 x LLN) decreased from 40.0% of subjects at baseline to 25.0% of subjects at EOT. Potentially clinically significantly low platelet values (defined as ≤ 0.6 x LLN) were observed throughout the study period, ranging from 53.3% at baseline to 45.8% of subjects at EOT.

Serum Chemistry:

The proportions of subjects with PCS elevated alkaline phosphatase and gamma-glutamyl transferase (GGT) values (each defined as ≥ 1.5 x ULN) throughout the study were of note. An elevated alkaline phosphatase value was observed for 24.1% of subjects at baseline, which increased to a maximum proportion of 59.1% at Day 7, with a further increase to 66.7% at EOT. Similarly, an elevated GGT value was observed for 46.2% of subjects at

baseline, which increased to a maximum proportion of 85.7% on Day 21, with a further increase to 89.5% at EOT. Of further interest, the proportions of subjects with PCS elevated alanine transaminase (ALT) and aspartate transaminase (AST) values (each defined as ≥ 3.0 x ULN) increased from baseline (0% and 3.4%, respectively) to a maximum proportion at Week 4 of 33.3% and 37.5%, respectively; at EOT, the proportions had decreased to 4.5% and 4.8%, respectively.

Electrocardiograms:

No clinically significant changes in cardiac conduction, cardiac rhythm or repolarization parameters were observed during study drug treatment.

Other Safety Results:

Vital signs, physical examination and X-ray results were used in adverse event assessment and were not reported separately.

CONCLUSION(S):

Although no definitive conclusions can be drawn from the results of this small, uncontrolled study, the data do not suggest any increased toxicity with the combination of anidulafungin and AmBisome in patients with invasive aspergillosis (IA). There were no differences in anidulafungin pharmacokinetics between subjects in this study, who received concomitant AmBisome, and subjects in other studies of anidulafungin. No relationship was observed between anidulafungin PK parameters and treatment outcome within the dosage used in this study. The AE profile and mortality rate were consistent with a critically ill population of patients with IA. The success rates in this trial are similar to those seen in historical data, although such a conclusion is confounded by differences in the populations studied in terms of disease severity, age, and other comorbidities from populations reported in earlier studies of IA. The detection of smaller differences would require the use of a larger sample size and contemporaneous controls, either well-matched to the study population or as part of a randomized study.