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

PROTOCOL NO.: A8851009

PROTOCOL TITLE: A Prospective, Randomized Trial Comparing the Efficacy of Anidulafungin and Voriconazole in Combination to That of Voriconazole Alone When Used for Primary Therapy of Proven or Probable Invasive Aspergillosis

Study Centers: Ninety-two (92) centers took part in the study and enrolled subjects; 16 in the United States, 12 in Germany, 8 in France, 7 in Italy, 5 each in the Korea Republic and Spain, 4 each in Belgium, Canada, the Russian Federation, 3 each in Brazil and Thailand, 2 each in Australia, Turkey, the United Kingdom, Poland, Portugal, Singapore, Switzerland and Taiwan, 1 each in the Czech Republic, Greece, India, Netherlands and Peru.

Study Initiation and Final Completion Dates: 09 July 2008 to 12 May 2011

Primary Completion Date: 08 April 2011

Phase of Development: Phase 3b

Study Objectives:

Primary Objective: To compare all-cause mortality at 6 weeks in subjects with hematologic malignancy or with allogeneic hematopoietic stem cell transplantation (HSCT) with a diagnosis of proven or probable invasive aspergillosis (IA) receiving voriconazole and anidulafungin in combination versus voriconazole monotherapy.

Secondary Objectives:

- To compare global response at 6 weeks;
- To compare mortality due to IA at 6 weeks;
- To compare all-cause mortality at 6 weeks in subjects with hematologic malignancy or with allogeneic HSCT with a diagnosis of possible, proven, or probable IA (Intent-to-Treat [ITT] population) receiving the combination of voriconazole and anidulafungin to voriconazole monotherapy;

- To compare all-cause mortality at 12 weeks in subjects with hematologic malignancy or with allogeneic HSCT with a diagnosis of proven or probable IA receiving the combination of voriconazole and anidulafungin to voriconazole monotherapy;

- To compare time to death due to IA in subjects with hematologic malignancy or with allogeneic HSCT with a diagnosis of proven or probable IA receiving the combination of voriconazole and anidulafungin to voriconazole monotherapy;

- To compare time to death (all cause) in subjects with hematologic malignancy or with allogeneic HSCT with a diagnosis of proven or probable IA receiving the combination of voriconazole and anidulafungin to voriconazole monotherapy;

- To compare the safety and tolerability of voriconazole monotherapy to that of voriconazole in combination with anidulafungin.

METHODS

Study Design: This double-blind, randomized study compared the efficacy and safety of voriconazole and anidulafungin in combination to voriconazole alone in allogeneic HSCT recipients and subjects with hematologic malignancies with proven or probable IA. Subjects with possible IA were enrolled in the study. However, these subjects were required to have a proven or probable diagnosis established within 7 days of enrollment. Subjects were stratified at study entry for host and transplant variables known to have an independent impact on the probability of death due to IA; these included: 1) allogeneic HSCT versus other; and 2) pulmonary IA versus other.

Subjects were to receive a total of 6 weeks of therapy. Subjects were randomized to 1 of 2 treatment arms: voriconazole and placebo for anidulafungin or voriconazole and active anidulafungin. After 2 weeks, the Investigator had the option of either continuing the subject's initial treatment regimen or switching the subject to voriconazole monotherapy. Subjects who were switched to voriconazole monotherapy had to demonstrate improvement in presenting clinical signs and symptoms and stable or improved radiographic response. For the final 2 weeks of treatment, all subjects received voriconazole monotherapy.

Voriconazole was to be administered in the intravenous (IV) formulation for the first week of therapy. Subsequently, subjects could be switched between IV and oral voriconazole at the discretion of the Investigator. Anidulafungin and anidulafungin placebo were administered IV.

Assessments of response to treatment were performed every 2 weeks during the study. Outcomes were assessed after 6 weeks of antifungal therapy. All-cause mortality was also assessed at the 12-week time point. The comparative design enabled evaluation of efficacy, safety, and tolerability of the combination regimen in a blinded, unbiased fashion. The schedule of study activities is presented in Table 1.

Table 1. Schedule of Activities

	Baseline	Treatment Period					Follow-Up
Weeks		**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6 or EOT**	**Week 12**
Days	**1**	**3 and 7±1**	**10 and 14±1**	**21±2**	**28±2**	**42+7**	**84+7**
Informed consent	X	-	-	-	-	-	-
Complete medical history and physical examination	X	-	-	-	-	X	-
Assessment of clinical signs and symptoms	X	X	X	X	X	X	-
Targeted interim history and physical examination	-	X	X	X	X	-	-
Laboratory							
Hematology	X	X	X	X	X	X	-
Blood chemistry	X	X	X	X	X	X	-
CYP 2C19 genotype testing	X	-	-	-	-	-	-
Galactomannan assay[a]	X[a]	X	X	X	X	X	-
Pharmacokinetics (1)[b]	X[c]	X	X (Day 14)	-	-	-	-
Pharmacokinetics for dosage adjustment (2)[d]		X[d]		X[d]			
Microbiology/histopathology	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[f]
Pregnancy test[g]	X	-	-	-	-	X	-
Aspergillus PCR (optional)	X	-	-	-	-	-	-
CT scan	X	-	X (Day 14)	-	X	X	-
Visual acuity (distance vision) test	X	X (Day 7)	X (Day 14)	X[h]	X	X[h]	X[h]
Assessment of visual symptoms[i]	X	X	X	X	X	X	X[j]
Ophthalmologic examination	X[k]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Registration/randomization	X	-	-	-	-	-	-
Study treatment							
Voriconazole monotherapy (Arm A)	X	X	X	X	X	X	-
Combination treatment (Arm B)	X	X	X	X	X	X	-
Assessments							
Survival	-	-	-	-	-	X	X
Evaluation of global response	-	-	X (Day 14)	-	X	X	-
Adverse event assessment	X	X	X	X	X	X	-
Concomitant medications	X	X	X	X	X	X	X[m]
Healthcare research utilization	X	X	X	X	X	X	-

Table 1. Schedule of Activities

CT = computed tomography; CYP = cytochrome P450; EOT = end-of-treatment; PCR = polymerase chain reaction.

a. Two specimens were to be collected at the baseline visit.

b. In a subset of subjects (100-150), two 3 mL blood samples were to be collected at 4 occasions during the study for anidulafungin and voriconazole measurement: Day 2: predose (just prior to the infusion of voriconazole in the morning); Day 3: postdose (ideally 0-3 hours following the end of infusion of voriconazole in the morning); Day 7: delayed postdose (ideally 6-10 hours following the end of infusion of voriconazole in the morning); Day 14: predose (just prior to the infusion of anidulafungin). Anidulafungin/placebo was preferred to be administered ahead of voriconazole in this subset.

c. For subjects who were receiving voriconazole prophylaxis only at the time of study entry (these subjects must have had proven or probable invasive aspergillosis to be enrolled). This specimen collected at the baseline visit (before the start of therapy) was to be used to assess prestudy voriconazole level only and was not included as part of the pharmacokinetic analysis. The timing of the last dose of voriconazole prophylaxis received was to be recorded in the case report form.

d. Recommended for all subjects to facilitate voriconazole dose adjustment: a blood sample for voriconazole measurement was to be collected at the end of intravenous voriconazole infusion on Day 3, and another blood sample was to be collected at approximately 1 to 2 hours after oral dosing on the third day after switching to oral voriconazole therapy. (Note: if the sample could not be collected on the recommended date due to a scheduling conflict, it could be collected at a later date).

e. If clinically indicated.

f. Culture collected, if clinically indicated.

g. For women of child-bearing potential. Pregnancy tests could also be repeated as per request of institutional review board/independent ethics committee or if required by local regulations.

h. Only if there had been a change in visual acuity or if new visual symptoms were reported by the subject.

i. A questionnaire was used to facilitate the monitoring of visual symptoms.

j. If visual symptoms were reported at Week 6.

k. Only the color vision test was performed before the start of study treatment on Day 1.

l. Color vision testing and dilated fundoscopic examination. To be performed only if there was a change in visual acuity or if visual symptoms were reported by the subject. If either of these conditions applied, follow-up had to be continued until symptoms resolved or Week 12, whichever occurred earlier.

m. Information regarding use of any systemic antifungal agents between Weeks 6 and 12 was collected.

Number of Subjects (Planned and Analyzed): A total of 405 subjects were planned to be enrolled to achieve a sample size of 250 evaluable subjects (125 per arm) completing the study. A total of 481 subjects were screened for participation in the study, of which 459 subjects were randomized to receive study treatment. A total of 454 subjects were treated and analyzed.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 16 years and older who were in immunocompromised state due to either receipt of hematopoeitic stem cell transplantation or hematologic malignancy and who had been diagnosed with proven, probable, or possible IA.

Study Treatment: Voriconazole, which was administered open-label, was supplied by local sites or by the study sponsor. Anidulafungin (lyophilized) and its companion diluents were supplied by the study sponsor and administered in a blinded manner. Subjects randomized to receive placebo for anidulafungin were infused IV with the contents of a stock infusion bag or bottle provided by each site.

Overall, subjects received 6 weeks of antifungal therapy. During the first 2 weeks of therapy, subjects randomized to the combination treatment group received voriconazole and anidulafungin. The dose for anidulafungin for all subjects was 200 mg IV on Day 1, followed by 100 mg IV once daily (QD) thereafter. Anidulafungin and placebo for anidulafungin were administered IV. During the first 2 weeks of therapy, subjects randomized to the voriconazole treatment group received voriconazole and placebo for anidulafungin. The placebo for anidulafungin was administered QD during the initial 2-week treatment period.

All subjects received IV or oral voriconazole and were treated with an initial loading dose and a subsequent maintenance dose based on body weight. IV voriconazole (200 mg IV infusion/vial) was required for all subjects during the first week of therapy. Subjects could subsequently switch to oral voriconazole (40 mg/mL suspension or 50 mg and 200 mg tablets), at the discretion of the Investigator after the first week. For subjects with estimated creatinine clearance <50 mL/minute, oral voriconazole was recommended after the initial 1-week treatment with IV voriconazole.

During the final 2 weeks of treatment, all subjects received maintenance voriconazole monotherapy.

Anidulafungin and anidulafungin placebo were to be administered within 2 hours before or after the scheduled administration time. Voriconazole was to be administered within 1 hour before or after the scheduled administration time. IV infusions of anidulafungin and voriconazole were administered sequentially.

Efficacy and Safety Endpoints:

Primary Endpoint:

The primary endpoint was all-cause mortality, measured 6 weeks after initiation of study drug in subjects with proven or probable IA.

Secondary Endpoints:

- Rate of global response at 6 weeks;
- All-cause mortality at 6 weeks in subjects with possible, probable or proven IA (ITT population);
- All-cause mortality at 12 weeks in subjects with probable or proven IA;
- Mortality due to IA at 6 weeks;
- Time to death (all-cause mortality);
- Time to death due to IA;
- Safety and tolerability of voriconazole monotherapy compared to that of voriconazole in combination with anidulafungin.

Safety Evaluations: Safety evaluations included adverse events (AEs), laboratory evaluations, and ophthalmological assessments.

Statistical Methods: The modified intent-to-treat (MITT) population was defined to be the set of all randomized subjects with proven or probable IA confirmed by Day 7 following enrollment, who had received at least 1 dose of study medication. The MITT population was the primary efficacy analysis population. The ITT and Per-Protocol (PP) populations were used in additional supportive analyses of efficacy.

The ITT analysis set consisted of the subjects in the MITT analysis set plus subjects with possible IA who could not be upgraded to probable or proven IA within 7 days and who had received at least 1 dose of study medication. The PP analysis set consisted of the subjects in the MITT population who had completed at least 2 weeks of study therapy, and it excluded those subjects with protocol violations that could have had an impact on the efficacy endpoints. Subjects who died within 2 weeks of starting on study therapy were included in the PP analysis set.

The primary efficacy endpoint was calculated using the Kaplan-Meier (KM) product limit estimator on Day 42 (6 weeks) within each stratum and weighted by the harmonic mean of the sample sizes in the strata. Time to death (T) was measured from the first dose of study medication in days, where T = (date of death – first treatment date + 1).

For secondary endpoints, rate of global response, defined as the number of subjects with a successful response ("complete" or "partial" global response as adjudicated by the data review committee [DRC]), was calculated as a percentage of all subjects (including subjects with "missing" response), at 6 weeks. Investigators also recorded a global response. Global response was programmatically determined as follows:

Success: A subject who achieved a "complete" or "partial" global response was categorized as a successful response; Failure: A subject was categorized as an unsuccessful response if

global response was “stable” or “failure” or if there was either a clinical failure or radiological failure.

All-cause mortality at 6 weeks in subjects with possible, probable, or proven IA, was calculated using the KM product limit estimator at Day 42 (Week 6). All-cause mortality at 12 weeks in subjects with probable or proven IA, was calculated using the KM product limit estimator at Day 84 (Week 12). Mortality due to IA at 6 weeks in subjects with probable or proven IA: Cause of death for this analysis was determined by the DRC. Subjects who died for causes other than IA before 6 weeks were censored at their time of death in this analysis. The mortality rates were calculated using the KM product limit estimator at Day 42 (Week 6). Time to death due to IA: Cause of death for this analysis was determined by the DRC. Subjects who died for causes other than IA were defined as censored at time of death.

The analysis of time-to-event endpoints was performed using the Cox proportional hazards model to calculate a meaningful summary parameter (hazard ratio). The model included terms for treatment group and randomization stratum.

The safety analysis set consisted of randomized subjects who took at least 1 dose of study medication. No formal statistical analyses were planned for safety data. The safety endpoints were listed and summarized using descriptive statistics.

RESULTS

Subject Disposition and Demography: A summary of subject disposition is presented in Table 2.

Table 2. Subject Disposition

Number (%) of Subjects	Voriconazole/ Anidulafungin	Voriconazole/ Placebo	Total
Screened (N=481)			
Assigned to study treatment	230	229	459
Treated	228 (100.0)	226 (100.0)	454 (100.0)
Completed study	154 (67.5)	146 (64.6)	300 (66.1)
Discontinued study	74 (32.5)	80 (35.4)	154 (33.9)
Subject died	68 (29.8)	71 (31.4)	-
Not related to study drug	6 (2.6)	9 (4.0)	-
Lost to follow-up	0	2 (0.9)	-
Other	0	1 (0.4)	-
Subject no longer willing to participate	6 (2.6)	6 (2.7)	-
Completed treatment	101 (44.3)	98 (43.4)	199 (43.8)
Discontinued treatment	127 (55.7)	128 (56.6)	255 (56.2)
Subject died	15 (6.6)	15 (6.6)	-
Related to study drug	48 (21.1)	45 (19.9)	-
Adverse event	38 (16.7)	34 (15.0)	-
Lack of efficacy	10 (4.4)	11 (4.9)	-
Not related to study drug	64 (28.1)	68 (30.1)	-
Adverse event	0	1 (0.4)	-
Global deterioration of health status	3 (1.3)	4 (1.8)	-
Other[a]	55 (24.1)	56 (24.8)	-
Protocol violation	0	1 (0.4)	-
Subject no longer willing to participate	4 (1.8)	5 (2.2)	-
Subject refused continued treatment for reason other than adverse event	2 (0.9)	1 (0.4)	-

Discontinuations occurring outside of the lag period were attributed to the last study treatment received.
N = number of subjects.
a. The majority of discontinuations due to "Other," not related to study drug, were due to failure to confirm a diagnosis of probable or proven invasive aspergillosis by Day 7.

A summary of data sets analyzed is presented in Table 3.

Table 3. Data Sets Analyzed

Number (%) of Subjects	Voriconazole/ Anidulafungin	Voriconazole/ Placebo	Total
Assigned to study treatment	230	229	459
Treated	228 (100)	226 (100)	454 (100)
Analyzed for efficacy			
ITT	215 (94.3)	207 (91.6)	422 (93.0)
MITT	135 (59.2)	142 (62.8)	277 (61.0)
PP	117 (51.3)	128 (56.6)	245 (54.0)
Number of subjects excluded from efficacy analysis	3 (1.3)	0	-
Excluded for site compliance[a]	3	0	-
Efficacy population	225 (98.7)	226 (100)	-
Number of subjects excluded from ITT population	10 (4.4)	19 (8.4)	-
Did not have possible, probable, or proven aspergillosis	10	19	-
Number of subjects excluded from MITT population	90 (40.0)	84 (37.2)	-
Excluded from ITT population	10 (11.1)	19 (22.6)	-
Had possible aspergillosis	80 (88.9)	65 (77.4)	-
Number of subjects excluded from PP population	108 (48.0)	98 (43.4)	-
Excluded from MITT population	90	84	-
Did not complete 2 weeks of study therapy	18	14	-
Analyzed for safety			
Adverse events	228 (100)	226 (100)	454 (100)
Laboratory data	224 (98.2)	223 (98.7)	447 (98.5)
Visual testing	199 (87.3)	197 (87.2)	396 (87.2)

ITT = intent-to-treat; MITT = modified intent-to-treat; PP = per-protocol.
a. Three subjects from one site were excluded from all efficacy analyses due to site compliance issues.

A summary of demographic and baseline characteristics for the MITT and ITT population is presented in Table 4.

Table 4. Demographic and Baseline Characteristics – Modified Intent-to-Treat Population and Intent-to-Treat Population

	Modified Intent-to-Treat Population		Intent-to-Treat Population	
	Voriconazole/ Anidulafungin N=135	Voriconazole/ Placebo N=142	Voriconazole/ Anidulafungin N=215	Voriconazole/ Placebo N=207
Number of subjects, n				
Male	74	82	125	122
Female	61	60	90	85
Age, years				
Mean (SD)	52.2 (14.9)	51.6 (15.4)	51.6 (15.6)	51.2 (15.9)
Range	18-79	18-83	18-83	17-83
Race, n (%)				
White	99 (73.3)	98 (69.0)	158 (73.5)	142 (68.6)
Black	3 (2.2)	3 (2.1)	5 (2.3)	3 (1.4)
Asian	31 (23.0)	35 (24.6)	47 (21.9)	53 (25.6)
Other	2 (1.5)	6 (4.2)	5 (2.3)	9 (4.3)
Body mass index, kg/m^2				
Mean (SD)	24.0 (5.1)	24.0 (4.8)	24.3 (5.0)	24.2 (4.8)
Range	12.9-41.0	16.2-44.9	12.9-41.0	14.9-47.3

Body mass index calculated as weight/(height * 0.01)^2.
N = number of subjects; n = number of subject in specified criteria; SD = standard deviation.

Efficacy Results:

Primary Efficacy Analysis: A summary of the analysis of all-cause mortality at Week 6 for the MITT population in subjects with proven or probable IA is presented in Table 5. All-cause mortality rates at Week 6 for the voriconazole/anidulafungin and voriconazole/placebo groups were 19.5% and 27.8%, respectively, in the MITT population. The difference in mortality rate adjusted for randomization strata was −8.74% (1-sided p=0.0434), with a 95% confidence interval of (−18.99%, 1.51%), with the voriconazole/anidulafungin group having lower mortality.

Table 5. Analysis of All-Cause Mortality at Week 6 – MITT Population

	Voriconazole/ Anidulafungin N=135	Voriconazole/ Placebo N=142
Number of deaths	26	39
Number of subjects alive at last observed time point up to Week 6	109	103
Alive at Week 6	106	101
Withdrew consent prior to Week 6	3	1
Discontinued prior to Week 6 (without follow-up date)	0	1
Subjects ongoing (censored prior to Week 6)	0	0
Unstratified analysis		
Mortality rate, %	19.5	27.8
Estimated treatment differences, %	-8.34	
95% CI for the differences	-18.35, 1.67	
p-value	0.0512	
Stratified analysis		
Estimated treatment differences, %	-8.74	
95% CI for the difference	-18.99, 1.51	
p-value	0.0434	

Mortality rate was based on the KM product limit estimator. Treatment difference (stratified) was based on a weighted difference in proportions. The 95% CI was based on using Greenwood's formula for the variance of the KM estimator. The p-value was based on a 1-sided test and was tested against a 1-sided alpha of 0.0223 to determine statistical significance. Stratification variables were site of infection and host factors.
CI = confidence interval; KM = Kaplan-Meier; MITT = modified intent-to-treat; N = number of subjects.

Secondary Efficacy Analysis: Analysis of successful global response in the MITT population as determined by the DRC at Week 6 with missing data treated as failure is presented in Table 6.

Table 6. Analysis of Successful Global Response (DRC) at Week 6 (Missing Data Treated as Failure) – MITT Population

	Voriconazole/ Anidulafungin N=135	Voriconazole/ Placebo N=142
Global response		
Number of successes	44	61
Number of failures	91	81
Unstratified analysis		
Success rate (%)	32.6	43.0
Estimated treatment differences (%)	-10.37	
95% CI for the differences	-21.71, 0.98	
p-value	0.0367	
Stratified analysis		
Estimated treatment differences (%)	-10.23	
95% CI for the differences	-21.6, 1.15	
p-value	0.0391	

Treatment difference (stratified) was based on a weighted difference in proportions. The 95% CI was based on the difference in success rates using the binomial variance. The p-value was based on a 1-sided z-test for the difference in response rates, adjusting for randomization strata, using the normal approximation to the binomial distribution. Stratification variables were site of infection and host factors.
CI = confidence interval; DRC = Data Review Committee; MITT = modified intent-to-treat; N = number of subjects.

A summary of the analysis of all-cause mortality at Weeks 6 (ITT population) and 12 (MITT population) is presented in Table 7.

Table 7. Analysis of All-Cause Mortality at Week 6 (ITT population) and Week 12 (MITT population)

	Week 6 - ITT Population		Week 12 - MITT Population	
	Voriconazole/ Anidulafungin N=215	Voriconazole/ Placebo N=207	Voriconazole/ Anidulafungin N=135	Voriconazole/ Placebo N=142
Number of deaths	44	47	39	55
Number of subjects alive at last observed time point up to Week 6	171	160	96	87
Alive at Week 6	166	154	93	84
Withdrew consent prior to Week 6	5	4	3	1
Discontinued prior to Week 6 (without follow-up date)	0	2	0	2
Subjects ongoing (censored prior to Week 6)	0	0	0	0
Unstratified analysis				
Mortality rate, %	20.7	23.1	29.3	39.4
Estimated treatment differences, %	-2.4		-10.01	
95% CI for the differences	-10.36, 5.56		-21.22, 1.21	
p-value	0.2773		0.0402	
Stratified analysis				
Estimated treatment differences, %	-2.6		-10.18	
95% CI for the difference	-10.77, 5.56		-21.44, 1.09	
p-value	0.2611		0.0383	

Mortality rate was based on the KM product limit estimator. Treatment difference (stratified) was based on a weighted difference in proportions. The 95% CI was based on using Greenwood's formula for the variance of the KM estimator. The p-value was based on a 1-sided test. Stratification variables were site of infection and host factors.
CI = confidence interval; ITT = intent-to-treat; KM = Kaplan-Meier; MITT = modified intent-to-treat; N = number of subjects.

A summary of the analysis of mortality due to IA at Week 6 for the MITT population (DRC adjudicated) is presented in Table 8.

Table 8. Analysis of Mortality Due to Invasive Aspergillosis (DRC Adjudicated) at Week 6 – MITT Population

	Voriconazole/ Anidulafungin N=135	Voriconazole/ Placebo N=142
Number of deaths	23	33
Number of subjects alive at last observed time point up to Week 6	112	109
Alive at Week 6	106	101
Withdrew consent prior to Week 6	3	2
Discontinued prior to Week 6 (without follow-up date)	3	6
Subjects ongoing (censored prior to Week 6)	0	0
Unstratified analysis		
Mortality rate, %	17.3	23.9
Estimated treatment differences, %	-6.61	
95% CI for the differences	-16.21, 2.98	
p-value	0.0884	
Stratified analysis		
Estimated treatment differences, %	-6.24	
95% CI for the difference	-15.9, 3.42	
p-value	0.1029	

Mortality rate was based on the KM product limit estimator. Treatment difference (stratified) was based on a weighted difference in proportions. The 95% CI was based on using Greenwood's formula for the variance of the KM estimator. The p-value was based on a 1-sided test. Stratification variables were site of infection and host factors.
CI = confidence interval; DRC = Data Review Committee; KM = Kaplan-Meier; MITT = modified intent-to-treat; N = number of subjects.

The median survival time for the 39 subjects who died in the MITT population from the start of treatment (all causes) in the voriconazole/anidulafungin group was 30 days and was also 30 days for the 55 subjects who died in the voriconazole/placebo group. The hazard of death in the voriconazole/anidulafungin group was lower than that in the voriconazole/placebo group (hazard ratio=0.696; 2-sided p=0.083).

A summary of the analysis of time to death due to IA from the start of treatment in the MITT population is presented in Table 9.

Table 9. Analysis of Time to Death Due to Invasive Aspergillosis From Start of Treatment – MITT Population

	Voriconazole/ Anidulafungin N=135		Voriconazole/ Placebo N=142
Subjects who died, n (%)	23 (17.0)		34 (23.9)
Median survival time, days	14.0		18.5
Range of survival time, days	2–40		4–45
Hazard ratio		0.687	
95% CI		0.40, 1.16	
p-value		0.164	

Analysis results based on Cox proportional hazards model. Subjects who died beyond Day 84 were censored.
CI = confidence interval; MITT = modified intent-to-treat; N = number of subjects.

Safety Results:

A summary of all-causality and treatment-related AEs is provided in Table 10. The majority of the AEs were considered to be unrelated to study treatment and were mild or moderate in severity. Treatment-emergent AEs that occurred in ≥5% of subjects in either treatment group are presented in Table 11.

Table 10. Overview of Treatment-Emergent Adverse Events

Number (%) of Subjects	Voriconazole/ Anidulafungin	Voriconazole/ Placebo
All Causalities		
Subjects evaluable for AEs	228	226
Number of AEs	1959	1877
Subjects with AEs	219 (96.1)	219 (96.9)
Subjects with SAEs[a]	115 (50.4)	104 (46.0)
Subjects with severe AEs	130 (57.0)	118 (52.2)
Subjects discontinued due to AEs[b]	12 (5.3)	16 (7.1)
Voriconazole Treatment-Related[c]		
Subjects evaluable for AEs	228	226
Number of AEs	233	187
Subjects with AEs	106 (46.5)	99 (43.8)
Subjects with SAEs	20 (8.8)	12 (5.3)
Subjects with severe AEs	34 (14.9)	16 (7.1)
Subjects discontinued due to AEs	7 (3.1)	7 (3.1)
Subjects discontinued voriconazole due to AEs	21 (9.2)	14 (6.2)
Subjects discontinued anidulafungin/placebo due to AEs	17 (7.5)	10 (4.4)
Subjects temporarily discontinued voriconazole due to AEs	5 (2.2)	3 (1.3)
Subjects temporarily discontinued anidulafungin/placebo due to AEs	2 (0.9)	1 (0.4)
Subjects with dose reduction of voriconazole due to AEs	24 (10.5)	12 (5.3)
Subjects with dose reduction of anidulafungin/placebo due to AEs	0	0
Anidulafungin/Placebo Treatment-Related[d]		
Subjects evaluable for AEs	228	226
Number of AEs	120	65
Subjects with AEs	53 (23.2)	42 (18.6)
Subjects with SAEs	11 (4.8)	8 (3.5)
Subjects with severe AEs	24 (10.5)	8 (3.5)
Subjects discontinued due to AEs	3 (1.3)	5 (2.2)
Subjects discontinued voriconazole due to AEs	10 (4.4)	8 (3.5)
Subjects discontinued anidulafungin/placebo due to AEs	6 (2.6)	7 (3.1)
Subjects temporarily discontinued voriconazole due to AEs	0	0
Subjects temporarily discontinued anidulafungin/placebo due to AEs	3 (1.3)	0
Subjects with dose reduction of voriconazole due to AEs	5 (2.2)	0
Subjects with dose reduction of anidulafungin/placebo due to AEs	0	0

Includes data up to 30 days after the 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. MedDRA (v14.1) coding dictionary was applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
a. SAEs were reported in the safety database for 13 additional subjects due to the following reasons: event occurred prior to the administration of study drug; event occurred after the administration of study drug was completed, which was within the reporting period for an SAE, but outside the reporting period for an AE; or subject was randomized but did not receive study drug.
b. Investigators and sites reported discontinuation information in 2 locations of the case report form: the AE page, Treatment Action item, and the End-of-Treatment Subject Summary page, Reason for Withdrawal item.
c. Includes only those AEs assessed by Investigator to be causally related to voriconazole treatment. Causality assessments were made by Investigators in a blinded manner without knowledge of treatment group.
d. Includes only those AEs assessed by Investigator to be causally related to anidulafungin treatment. Causality assessments were made by Investigators in a blinded manner without knowledge of treatment group; hence anidulafungin related AEs were recorded in the voriconazole/placebo treatment arm.

Table 11. Summary of Treatment-Emergent Adverse Events (All Causalities) in ≥5% of Subjects in Either Treatment Group

System Organ Class Preferred Term	Voriconazole/Anidulafungin N=228 n (%)	Voriconazole/Placebo N=226 n (%)
Blood and lymphatic system disorders	36 (15.8)	43 (19.0)
Anemia	9 (3.9)	13 (5.8)
Febrile neutropenia	6 (2.6)	14 (6.2)
Cardiac disorders	43 (18.9)	45 (19.9)
Tachycardia	14 (6.1)	21 (9.3)
Eye disorders	49 (21.5)	58 (25.7)
Vision blurred	14 (6.1)	11 (4.9)
Gastrointestinal disorders	130 (57.0)	133 (58.8)
Abdominal pain	14 (6.1)	13 (5.8)
Abdominal pain upper	9 (3.9)	15 (6.6)
Constipation	35 (15.4)	30 (13.3)
Diarrhea	39 (17.1)	40 (17.7)
Dyspepsia	6 (2.6)	12 (5.3)
Nausea	38 (16.7)	42 (18.6)
Vomiting	33 (14.5)	24 (10.6)
General disorders and administration site conditions	120 (52.6)	127 (56.2)
Chest pain	17 (7.5)	9 (4.0)
Chills	13 (5.7)	10 (4.4)
Fatigue	6 (2.6)	14 (6.2)
Mucosal inflammation	10 (4.4)	15 (6.6)
Edema	12 (5.3)	14 (6.2)
Edema peripheral	34 (14.9)	34 (15.0)
Pain	10 (4.4)	13 (5.8)
Pyrexia	31 (13.6)	46 (20.4)
Infections and infestations	105 (46.1)	99 (43.8)
Pneumonia	10 (4.4)	12 (5.3)
Sepsis	14 (6.1)	12 (5.3)
Septic shock	11 (4.8)	16 (7.1)
Injury, poisoning and procedural complications	35 (15.4)	22 (9.7)
Fall	13 (5.7)	4 (1.8)
Investigations	78 (34.2)	67 (29.6)
Aspartate aminotransferase increased	12 (5.3)	13 (5.8)
Blood alkaline phosphatase increased	20 (8.8)	6 (2.7)
Metabolism and nutrition disorders	91 (39.9)	82 (36.3)
Decreased appetite	15 (6.6)	14 (6.2)
Hypokalemia	37 (16.2)	31 (13.7)
Hypomagnesemia	18 (7.9)	15 (6.6)
Musculoskeletal and connective tissue disorders	50 (21.9)	44 (19.5)
Back pain	13 (5.7)	12 (5.3)
Pain in extremity	16 (7.0)	11 (4.9)
Nervous system disorders	65 (28.5)	62 (27.9)
Headache	16 (7.0)	26 (11.5)
Psychiatric disorders	77 (33.8)	73 (32.3)
Agitation	13 (5.7)	7 (3.1)
Anxiety	12 (5.3)	15 (6.6)
Confusional state	10 (4.4)	16 (7.1)
Hallucination, visual	8 (3.5)	12 (5.3)
Insomnia	29 (12.7)	22 (9.7)
Respiratory, thoracic and mediastinal disorders	110 (48.2)	106 (46.9)

Table 11. Summary of Treatment-Emergent Adverse Events (All Causalities) in ≥5% of Subjects in Either Treatment Group

System Organ Class Preferred Term	Voriconazole/Anidulafungin N=228 n (%)	Voriconazole/Placebo N=226 n (%)
Cough	16 (7.0)	22 (9.7)
Dyspnea	15 (6.6)	28 (12.4)
Epistaxis	20 (8.8)	20 (8.8)
Hemoptysis	12 (5.3)	9 (4.0)
Respiratory failure	13 (5.7)	15 (6.6)
Skin and subcutaneous tissue disorders	83 (36.4)	79 (35.0)
Petechiae	5 (2.2)	12 (5.3)
Rash	30 (13.2)	31 (13.7)
Vascular disorders	76 (33.3)	54 (23.9)
Hypertension	32 (14.0)	21 (9.3)
Hypotension	32 (14.0)	20 (8.8)

AEs and SAEs are not separated out.
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.
Includes data up to 30 days after the last dose of study drug.
MedDRA (v14.1) coding dictionary was applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with specified AE; SAE = serious adverse event.

Treatment-emergent AEs considered to be related to voriconazole and anidulafungin or placebo that occurred in ≥2% of subjects in either treatment group are presented in Table 12. The most common treatment emergent AEs considered to be related to study treatment included primarily AEs from the system organ class of investigations (alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased, blood alkaline phosphatase increased, and gamma-glutamyl transpeptidase [GGT] increased).

Table 12. Summary of Treatment-Emergent Treatment Related Adverse Events in ≥2% of Subjects in Either Treatment Group

System Organ Class Preferred Term	Voriconazole/ Anidulafungin N=228 n (%)	Voriconazole/ Placebo N=226 n (%)
Voriconazole Treatment Related		
Eye disorders	21 (9.2)	30 (13.3)
Vision blurred	6 (2.6)	9 (4.0)
Visual impairment	7 (3.1)	10 (4.4)
Gastrointestinal disorders	15 (6.6)	8 (3.5)
Nausea	8 (3.5)	2 (0.9)
Vomiting	6 (2.6)	1 (0.4)
Hepatobiliary disorders	21 (9.2)	8 (3.5)
Hyperbilirubinemia	8 (3.5)	1 (0.4)
Investigations	42 (18.4)	32 (14.2)
Alanine aminotransferase increased	11 (4.8)	7 (3.1)
Aspartate aminotransferase increased	11 (4.8)	9 (4.0)
Blood alkaline phosphatase increased	17 (7.5)	6 (2.7)
Gamma glutamyl transferase increased	10 (4.4)	9 (4.0)
Liver function test abnormal	7 (3.1)	3 (1.3)
Transaminases increased	7 (3.1)	2 (0.9)
Metabolism and nutrition disorders	9 (3.9)	4 (1.8)
Hypokalemia	5 (2.2)	1 (0.4)
Psychiatric disorders	22 (9.6)	25 (11.1)
Confusional state	3 (1.3)	5 (2.2)
Hallucination	9 (3.9)	8 (3.5)
Hallucination, visual	6 (2.6)	8 (3.5)
Skin and subcutaneous tissue disorders	9 (3.9)	12 (5.3)
Rash	6 (2.6)	6 (2.7)
Anidulafungin/Placebo Treatment Related		
Gastrointestinal disorders	12 (5.3)	8 (3.5)
Nausea	6 (2.6)	3 (1.3)
Investigations	22 (9.6)	15 (6.6)
Alanine aminotransferase increased	7 (3.1)	1 (0.4)
Aspartate aminotransferase increased	7 (3.1)	3 (1.3)
Blood alkaline phosphatase increased	12 (5.3)	2 (0.9)
Gamma glutamyl transferase increased	6 (2.6)	6 (2.7)
Nervous system disorders	12 (5.3)	1 (0.4)
Headache	5 (2.2)	0
Skin and subcutaneous tissue disorders	7 (3.1)	5 (2.2)
Rash	5 (2.2)	4 (1.8)

AEs and SAEs are not separated out.
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. Includes data up to 30 days after the last dose of study drug.
MedDRA (v14.1) coding dictionary was applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with specified AE; SAE = serious adverse event.

Serious AEs (SAEs) reported during the study are presented in Table 13. The most commonly reported SAEs were aspergillosis, disease progression, febrile neutropenia, respiratory failure, sepsis, and septic shock. None of these SAEs were considered by the Investigator to be treatment related.

Table 13. Serious Adverse Events

Number (%) of Subjects MedDRA Preferred Term	Voriconazole/ Anidulafungin N=228	Voriconazole/ Placebo N=226
Any number of subjects with serious adverse events	120 (52.6)	112 (49.6)
Abdominal pain	1 (0.4)	1 (0.4)
Acute leukemia	1 (0.4)	0
Acute lung injury	0	1 (0.4)
Acute lymphocytic leukemia	1 (0.4)	1 (0.4)
Acute lymphocytic leukemia recurrent	1 (0.4)	0
Acute myeloid leukemia	5 (2.2)	4 (1.8)
Acute respiratory distress syndrome	2 (0.9)	4 (1.8)
Acute respiratory failure	3 (1.3)	1 (0.4)
Anemia	2 (0.9)	0
Anaplastic large cell lymphoma T- and null-cell types	1 (0.4)	0
Aortic occlusion	1 (0.4)	0
Aphasia	0	1 (0.4)
Arrhythmia	0	1 (0.4)
Arthralgia	1 (0.4)	0
Ascites	0	1 (0.4)
Aspergillosis	7 (3.1)	7 (3.1)
Asthenia	0	2 (0.9)
Atrial fibrillation	5 (2.2)	3 (1.3)
Bacteremia	2 (0.9)	0
Bacterial sepsis	1 (0.4)	0
Blast crisis in myelogenous leukemia	1 (0.4)	0
Blindness	1 (0.4)	0
Blindness unilateral	1 (0.4)	0
Blood creatine phosphokinase increased	1 (0.4)	0
Bradycardia	1 (0.4)	0
Brain herniation	0	1 (0.4)
Bronchopulmonary aspergillosis	1 (0.4)	0
Bronchospasm	1 (0.4)	0
C-reactive protein increased	1 (0.4)	1 (0.4)
Cardiac arrest	2 (0.9)	1 (0.4)
Cardio-respiratory arrest	0	1 (0.4)
Cardiopulmonary failure	1 (0.4)	0
Central nervous system lesion	0	1 (0.4)
Central nervous system lymphoma	1 (0.4)	0
Cerebral hemorrhage	2 (0.9)	1 (0.4)
Cerebral infarction	1 (0.4)	1 (0.4)
Chest pain	1 (0.4)	0
Cholecystitis	0	1 (0.4)
Cholecystitis acute	0	2 (0.9)
Chronic lymphocytic leukemia	2 (0.9)	0
Chronic lymphocytic leukemia recurrent	1 (0.4)	0
Condition aggravated	1 (0.4)	2 (0.9)
Confusional state	0	1 (0.4)
Convulsion	4 (1.8)	3 (1.3)
Cough	1 (0.4)	0
Cystitis hemorrhagic	1 (0.4)	0
Cytomegalovirus infection	1 (0.4)	1 (0.4)
Cytomegalovirus test positive	1 (0.4)	0
Death	1 (0.4)	2 (0.9)
Device related infection	1 (0.4)	0

Table 13. Serious Adverse Events

Number (%) of Subjects MedDRA Preferred Term	Voriconazole/ Anidulafungin N=228	Voriconazole/ Placebo N=226
Device related sepsis	0	1 (0.4)
Diarrhea	0	3 (1.3)
Disease progression	8 (3.5)	8 (3.5)
Disseminated intravascular coagulation	1 (0.4)	0
Disseminated tuberculosis	1 (0.4)	0
Dizziness	1 (0.4)	0
Drug interaction	1 (0.4)	0
Duodenal ulcer hemorrhage	1 (0.4)	0
Dyspnoea	3 (1.3)	4 (1.8)
Electrocardiogram QT prolonged	1 (0.4)	0
Encephalopathy	1 (0.4)	2 (0.9)
Endocarditis	0	1 (0.4)
Enterococcal bacteremia	1 (0.4)	0
Enterococcal sepsis	1 (0.4)	0
Escherichia sepsis	1 (0.4)	0
Extrasystoles	1 (0.4)	0
Fecaloma	1 (0.4)	0
Fall	1 (0.4)	0
Fatigue	1 (0.4)	0
Febrile neutropenia	2 (0.9)	7 (3.1)
Fungal infection	1 (0.4)	1 (0.4)
Gastric hemorrhage	1 (0.4)	0
Gastroenteritis	1 (0.4)	0
Gastrointestinal hemorrhage	1 (0.4)	2 (0.9)
General physical health deterioration	1 (0.4)	2 (0.9)
Genital ulceration	0	1 (0.4)
Graft versus host disease	0	1 (0.4)
Grand mal convulsion	1 (0.4)	1 (0.4)
Hematemesis	1 (0.4)	0
Hematological malignancy	0	1 (0.4)
Hematoma	1 (0.4)	0
Hemoptysis	3 (1.3)	3 (1.3)
Hallucination, visual	1 (0.4)	0
Hallucinations, mixed	1 (0.4)	0
Hepatic encephalopathy	1 (0.4)	0
Hepatic enzyme increased	0	1 (0.4)
Hepatic failure	1 (0.4)	0
Hepatic function abnormal	0	1 (0.4)
Hepatic infection fungal	1 (0.4)	0
Hepatotoxicity	1 (0.4)	0
Herpes zoster	2 (0.9)	0
Hydronephrosis	1 (0.4)	0
Hydropneumothorax	0	1 (0.4)
Hyperbilirubinemia	1 (0.4)	0
Hypercapnia	2 (0.9)	0
Hypoesthesia	1 (0.4)	0
Hypoglycaemia	0	1 (0.4)
Hypokalemia	0	1 (0.4)
Hyponatremia	0	1 (0.4)
Hypotension	2 (0.9)	1 (0.4)
Hypovolemia	1 (0.4)	0

Table 13. Serious Adverse Events

Number (%) of Subjects MedDRA Preferred Term	Voriconazole/ Anidulafungin N=228	Voriconazole/ Placebo N=226
Hypoxia	2 (0.9)	4 (1.8)
Ileitis	0	1 (0.4)
Ileus paralytic	1 (0.4)	0
Iliac artery thrombosis	0	1 (0.4)
Infection	1 (0.4)	0
Influenza	1 (0.4)	0
Ischemic stroke	0	1 (0.4)
Klebsiella bacteremia	1 (0.4)	0
Lactic acidosis	2 (0.9)	0
Leukemia	1 (0.4)	1 (0.4)
Leukemia plasmacytic	1 (0.4)	0
Leukemia recurrent	0	1 (0.4)
Lipase increased	0	1 (0.4)
Liver disorder	1 (0.4)	0
Liver function test abnormal	2 (0.9)	1 (0.4)
Liver injury	1 (0.4)	0
Loss of consciousness	0	1 (0.4)
Lower respiratory tract infection	1 (0.4)	0
Lung abscess	0	1 (0.4)
Lung infiltration	0	1 (0.4)
Lymphoma	4 (1.8)	1 (0.4)
Megacolon	1 (0.4)	0
Meningitis fungal	1 (0.4)	0
Metabolic acidosis	2 (0.9)	0
Multi-organ failure	5 (2.2)	4 (1.8)
Multiple myeloma	0	2 (0.9)
Myelodysplastic syndrome	0	1 (0.4)
Myocardial ischemia	0	1 (0.4)
Nephritic syndrome	1 (0.4)	0
Neuropathy peripheral	0	1 (0.4)
Neutropenia	0	3 (1.3)
Neutropenic colitis	1 (0.4)	0
Neutropenic sepsis	1 (0.4)	0
Non-Hodgkin's lymphoma	1 (0.4)	0
Non-Hodgkin's lymphoma refractory	0	1 (0.4)
Oliguria	1 (0.4)	1 (0.4)
Oral herpes	0	1 (0.4)
Oxygen saturation decreased	0	1 (0.4)
Pancytopenia	0	3 (1.3)
Pericardial effusion	1 (0.4)	0
Pleural effusion	2 (0.9)	2 (0.9)
Pneumocystis jiroveci pneumonia	0	1 (0.4)
Pneumonia	5 (2.2)	5 (2.2)
Pneumonia staphylococcal	0	1 (0.4)
Pneumonitis	1 (0.4)	0
Procalcitonin increased	0	1 (0.4)
Prostate cancer	1 (0.4)	0
Pulmonary alveolar hemorrhage	0	2 (0.9)
Pulmonary embolism	1 (0.4)	1 (0.4)
Pulmonary hemorrhage	2 (0.9)	0
Pulmonary infarction	0	1 (0.4)

Table 13. Serious Adverse Events

Number (%) of Subjects MedDRA Preferred Term	Voriconazole/ Anidulafungin N=228	Voriconazole/ Placebo N=226
Pulmonary edema	0	2 (0.9)
Pulmonary sepsis	1 (0.4)	0
Pulseless electrical activity	1 (0.4)	0
Pyrexia	4 (1.8)	5 (2.2)
Renal failure	2 (0.9)	1 (0.4)
Renal failure acute	6 (2.6)	1 (0.4)
Renal impairment	1 (0.4)	2 (0.9)
Respiratory disorder	0	1 (0.4)
Respiratory distress	3 (1.3)	6 (2.7)
Respiratory failure	15 (6.6)	15 (6.6)
Sepsis	9 (3.9)	10 (4.4)
Septic shock	10 (4.4)	14 (6.2)
Shock	2 (0.9)	1 (0.4)
Shock hemorrhagic	1 (0.4)	0
Sinusitis	0	1 (0.4)
Small intestinal obstruction	0	1 (0.4)
Staphylococcal bacteremia	0	1 (0.4)
Staphylococcal infection	0	1 (0.4)
Stomatitis	1 (0.4)	0
Streptococcal sepsis	1 (0.4)	0
Subclavian vein thrombosis	1 (0.4)	0
Subdural hematoma	1 (0.4)	0
Sudden cardiac death	0	1 (0.4)
Supraventricular tachycardia	1 (0.4)	1 (0.4)
Syncope	0	1 (0.4)
Systemic candida	1 (0.4)	0
Tachycardia	2 (0.9)	2 (0.9)
Tachypnea	0	1 (0.4)
Thrombotic microangiopathy	0	1 (0.4)
Thrombotic thrombocytopenic purpura	2 (0.9)	0
Transaminases increased	0	1 (0.4)
Tuberculosis	1 (0.4)	0
Upper gastrointestinal hemorrhage	1 (0.4)	0
Vaginal hemorrhage	1 (0.4)	0
Venoocclusive liver disease	1 (0.4)	0
Ventricular fibrillation	1 (0.4)	0
Vomiting	1 (0.4)	1 (0.4)
Wound	1 (0.4)	0
Zygomycosis	1 (0.4)	0

MedDRA (v14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.

Seventy-two subjects in the voriconazole/anidulafungin group and 73 subjects in the voriconazole/placebo group died due to AEs during the study (Table 14). Of the deaths reported, only those due to aspergillosis (2 events in the voriconazole/placebo group) and pneumonia (1 event in the voriconazole/placebo group) were considered to be treatment related.

Table 14. Deaths Due to Adverse Events

Number (%) of Subjects Cause of Death MedDRA Preferred Term	Voriconazole/ Anidulafungin N=228	Voriconazole/ Placebo N=226
Any number of subjects died due to serious adverse events	72 (31.6)	73 (32.3)
Abdominal pain	1 (0.4)	0
Acute leukemia	1 (0.4)	0
Acute lung injury	0	1 (0.4)
Acute lymphocytic leukemia	1 (0.4)	1 (0.4)
Acute myeloid leukemia	5 (2.2)	4 (1.8)
Acute respiratory distress syndrome	1 (0.4)	3 (1.3)
Acute respiratory failure	3 (1.3)	0
Anaemia	1 (0.4)	0
Anaplastic large cell lymphoma T- and null-cell types	1 (0.4)	0
Aortic occlusion	1 (0.4)	0
Aphasia	0	1 (0.4)
Arrhythmia	0	1 (0.4)
Ascites	0	1 (0.4)
Aspergillosis	6 (2.6)	6 (2.7)
Asthenia	0	1 (0.4)
Atrial fibrillation	2 (0.9)	2 (0.9)
Bacteremia	2 (0.9)	0
Bacterial sepsis	1 (0.4)	0
Blast crisis in myelogenous leukemia	1 (0.4)	0
Blindness	1 (0.4)	0
Blindness unilateral	1 (0.4)	0
Bradycardia	1 (0.4)	0
Brain herniation	0	1 (0.4)
Bronchopulmonary aspergillosis	1 (0.4)	0
Bronchospasm	1 (0.4)	0
Cardiac arrest	2 (0.9)	1 (0.4)
Cardio-respiratory arrest	0	1 (0.4)
Cardiopulmonary failure	1 (0.4)	0
Central nervous system lesion	0	1 (0.4)
Central nervous system lymphoma	1 (0.4)	0
Cerebral hemorrhage	1 (0.4)	1 (0.4)
Cerebral infarction	0	1 (0.4)
Chronic lymphocytic leukemia	2 (0.9)	0
Chronic lymphocytic leukemia recurrent	1 (0.4)	0
Condition aggravated	0	1 (0.4)
Confusional state	0	1 (0.4)
Convulsion	3 (1.3)	3 (1.3)
Cytomegalovirus infection	0	1 (0.4)
Death	1 (0.4)	2 (0.9)
Device related infection	1 (0.4)	0
Diarrhoea	0	2 (0.9)
Disease progression	8 (3.5)	8 (3.5)
Disseminated intravascular coagulation	1 (0.4)	0
Dyspnea	1 (0.4)	3 (1.3)
Encephalopathy	1 (0.4)	0
Endocarditis	0	1 (0.4)
Enterococcal bacteremia	1 (0.4)	0
Enterococcal sepsis	1 (0.4)	0
Escherichia sepsis	1 (0.4)	0

Table 14. Deaths Due to Adverse Events

Number (%) of Subjects Cause of Death MedDRA Preferred Term	Voriconazole/ Anidulafungin N=228	Voriconazole/ Placebo N=226
Fecaloma	1 (0.4)	0
Febrile neutropenia	1 (0.4)	2 (0.9)
Fungal infection	1 (0.4)	1 (0.4)
Gastric hemorrhage	1 (0.4)	0
Gastrointestinal hemorrhage	1 (0.4)	1 (0.4)
General physical health deterioration	1 (0.4)	2 (0.9)
Graft versus host disease	0	1 (0.4)
Grand mal convulsion	1 (0.4)	0
Hematological malignancy	0	1 (0.4)
Hemoptysis	0	1 (0.4)
Hallucination, visual	1 (0.4)	0
Hepatic encephalopathy	1 (0.4)	0
Hepatic enzyme increased	0	1 (0.4)
Hepatic failure	1 (0.4)	0
Hepatic function abnormal	0	1 (0.4)
Hepatic infection fungal	1 (0.4)	0
Hepatotoxicity	1 (0.4)	0
Hyperbilirubinemia	1 (0.4)	0
Hypercapnia	1 (0.4)	0
Hypoglycemia	0	1 (0.4)
Hypokalemia	0	1 (0.4)
Hyponatremia	0	1 (0.4)
Hypotension	1 (0.4)	1 (0.4)
Hypoxia	1 (0.4)	2 (0.9)
Ileitis	0	1 (0.4)
Ileus paralytic	1 (0.4)	0
Iliac artery thrombosis	0	1 (0.4)
Infection	1 (0.4)	0
Influenza	1 (0.4)	0
Lactic acidosis	-	0
Leukemia	1 (0.4)	1 (0.4)
Leukemia plasmacytic	1 (0.4)	0
Leukemia recurrent	0	1 (0.4)
Liver function test abnormal	2 (0.9)	1 (0.4)
Liver injury	1 (0.4)	0
Loss of consciousness	0	1 (0.4)
Lung infiltration	0	1 (0.4)
Lymphoma	4 (1.8)	1 (0.4)
Megacolon	1 (0.4)	0
Meningitis fungal	1 (0.4)	0
Metabolic acidosis	2 (0.9)	0
Multi-organ failure	5 (2.2)	4 (1.8)
Multiple myeloma	0	2 (0.9)
Myelodysplastic syndrome	0	1 (0.4)
Neutropenia	0	2 (0.9)
Neutropenic colitis	1 (0.4)	0
Non-Hodgkin's lymphoma	1 (0.4)	0
Non-Hodgkin's lymphoma refractory	0	1 (0.4)
Oliguria	1 (0.4)	1 (0.4)
Oxygen saturation decreased	0	1 (0.4)
Pleural effusion	0	1 (0.4)

Table 14. Deaths Due to Adverse Events

Number (%) of Subjects Cause of Death MedDRA Preferred Term	Voriconazole/ Anidulafungin N=228	Voriconazole/ Placebo N=226
Pneumocystis jiroveci pneumonia	0	1 (0.4)
Pneumonia	3 (1.3)	5 (2.2)
Pneumonia staphylococcal	0	1 (0.4)
Prostate cancer	1 (0.4)	0
Pulmonary alveolar hemorrhage	0	1 (0.4)
Pulmonary embolism	1 (0.4)	0
Pulmonary hemorrhage	2 (0.9)	0
Pulmonary edema	0	1 (0.4)
Pulmonary sepsis	1 (0.4)	0
Pulseless electricity activity	1 (0.4)	0
Pyrexia	1 (0.4)	1 (0.4)
Renal failure	2 (0.9)	1 (0.4)
Renal failure acute	5 (2.2)	1 (0.4)
Renal impairment	1 (0.4)	2 (0.9)
Respiratory disorder	0	1 (0.4)
Respiratory distress	2 (0.9)	3 (1.3)
Respiratory failure	12 (5.3)	14 (6.2)
Sepsis	5 (2.2)	6 (2.7)
Septic shock	6 (2.6)	10 (4.4)
Shock	2 (0.9)	1 (0.4)
Shock hemorrhagic	1 (0.4)	0
Staphylococcal bacteremia	0	1 (0.4)
Subclavian vein thrombosis	1 (0.4)	0
Subdural hematoma	1 (0.4)	0
Sudden cardiac death	0	1 (0.4)
Supraventricular tachycardia	0	1 (0.4)
Tachycardia	1 (0.4)	2 (0.9)
Tachypnea	0	1 (0.4)
Thrombotic microangiopathy	0	1 (0.4)
Thrombotic thrombocytopenic purpura	1 (0.4)	0
Transaminases increased	0	1 (0.4)
Tuberculosis	1 (0.4)	0
Upper gastrointestinal hemorrhage	1 (0.4)	0
Vaginal hemorrhage	1 (0.4)	0
Vomiting	0	1 (0.4)

MedDRA (v14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.

The permanent subject discontinuations from treatment due to AEs are presented in Table 15.

Table 15. Adverse Events Leading to Discontinuation From Treatment

Number (%) of Subjects MedDRA Preferred Term	Voriconazole/ Anidulafungin N=228	Voriconazole/ Placebo N=226
Any number of subjects with adverse events leading to discontinuation from treatment	38 (16.7)	34 (15.0)
Acute lymphocytic leukaemia	0	1 (0.4)
Alanine aminotransferase abnormal	0	1 (0.4)
Alanine aminotransferase increased	1 (0.4)	0
Aphasia	0	1 (0.4)
Arrhythmia	0	1 (0.4)
Aspartate aminotransferase increased	1 (0.4)	0
Aspergillosis	1 (0.4)	2 (0.9)
Atrial fibrillation	1 (0.4)	0
B-cell lymphoma refractory	0	1 (0.4)
Blindness	1 (0.4)	0
Blood bilirubin increased	0	1 (0.4)
Blood creatine phosphokinase increased	1 (0.4)	0
Bronchopulmonary aspergillosis	1 (0.4)	0
Candidiasis	0	1 (0.4)
Confusional state	1 (0.4)	1 (0.4)
Convulsion	0	1 (0.4)
Disseminated intravascular coagulation	1 (0.4)	0
Encephalopathy	0	1 (0.4)
Endocarditis	0	1 (0.4)
Epilepsy	0	1 (0.4)
Fungal infection	0	1 (0.4)
General physical health deterioration	1 (0.4)	0
H1N1 influenza	1 (0.4)	0
Hallucination	1 (0.4)	1 (0.4)
Hallucination, auditory	0	1 (0.4)
Hallucination, visual	1 (0.4)	0
Hepatic enzyme increased	1 (0.4)	3 (1.3)
Hepatic failure	1 (0.4)	0
Hepatic function abnormal	1 (0.4)	0
Hepatic vein occlusion	1 (0.4)	0
Hepatitis toxic	1 (0.4)	0
Hepatotoxicity	2 (0.9)	0
Hyperbilirubinemia	1 (0.4)	0
Hypoxia	0	1 (0.4)
Lactic acidosis	1 (0.4)	0
Leukemia plasmacytic	1 (0.4)	0
Liver disorder	1 (0.4)	0
Liver function test abnormal	1 (0.4)	1 (0.4)
Lung infiltration	0	1 (0.4)
Mental status changes	1 (0.4)	0
Multi-organ failure	0	1 (0.4)
Nephritic syndrome	1 (0.4)	0
Nephropathy toxic	0	1 (0.4)
Oliguria	1 (0.4)	0
Petit mal epilepsy	1 (0.4)	0
Pneumonia	2 (0.9)	2 (0.9)
Pneumonitis	1 (0.4)	0
Pulmonary edema	0	1 (0.4)
Rash	1 (0.4)	1 (0.4)

Table 15. Adverse Events Leading to Discontinuation From Treatment

Number (%) of Subjects MedDRA Preferred Term	Voriconazole/ Anidulafungin N=228	Voriconazole/ Placebo N=226
Renal failure acute	1 (0.4)	0
Respiratory disorder	1 (0.4)	0
Respiratory failure	0	1 (0.4)
Restlessness	1 (0.4)	0
Sepsis	1 (0.4)	0
Septic shock	1 (0.4)	2 (0.9)
Tachycardia	1 (0.4)	0
Thrombotic thrombocytopenic purpura	1 (0.4)	0
Transaminases increased	0	1 (0.4)
Tuberculosis	1 (0.4)	0
Zygomycosis	1 (0.4)	2 (0.9)

MedDRA (v14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.

No subjects permanently discontinued from the study due to AEs.

Thirty-five subjects in the voriconazole/anidulafungin group and 20 subjects in the voriconazole/placebo group had dose reductions or temporarily discontinued the study due to AEs. The majority of AEs leading to dose reductions or temporary discontinuations were moderate in severity and resolved.

Median changes from baseline in laboratory parameters were generally minimal and similar between treatment groups.

The majority of subjects had no visual acuity changes, changes in visual symptoms, changes in color vision defects, or changes in fundoscopy assessments from baseline.

CONCLUSIONS:

- The rates of all-cause mortality at Week 6 in the MITT population were 19.5% and 27.8% in the voriconazole/anidulafungin and voriconazole/placebo groups, respectively. The trend toward improved survival in the voriconazole/anidulafungin group did not achieve the prespecified level of statistical significance.

- Additional mortality analyses generally demonstrated survival advantages for the voriconazole/anidulafungin group for all secondary endpoints, though none of them were statistically significant. Of the prespecified subgroup analyses, statistically significant lower mortality in the voriconazole/anidulafungin group was observed in the subgroup of subjects who were non-neutropenic at Baseline. For other subgroups, the differences were not statistically significant.

- DRC-adjudicated global response in the MITT population at Week 6 was successful in 32.6% of the subjects in the voriconazole/anidulafungin group and 43.0% of the subjects in the voriconazole/placebo group, with the trend in favor of monotherapy. This was

divergent from the trend toward a survival advantage in the voriconazole/anidulafungin group.

- Based on the safety data, it was concluded that the combination of voriconazole and anidulafungin has an acceptable safety profile for the treatment of IA in adult subjects with allogeneic stem cell transplants and hematologic malignancies.