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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Vfend® / Voriconazole

PROTOCOL NO.: A1501038

PROTOCOL TITLE: Prospective, Open-Label, Non-Comparative, Multicenter Study for the Secondary Prophylaxis of Invasive Fungal Infections (IFI) With Voriconazole in Patients With Allogeneic Stem Cell Transplants

Study Centers: A total of 17 centers took part in the study and randomized subjects: 1 each in Belgium, Portugal, Sweden, and Switzerland; 5 in France; 3 each in Germany and Spain; and 2 in the United Kingdom (UK).

Study Initiation Date and Final Completion Date: 07 February 2005 to 04 April 2008

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

To evaluate the efficacy of voriconazole as secondary prophylaxis on the rate of occurrence of proven and probable IFI in allogeneic stem cell transplant (SCT) subjects having any underlying hematological disease with previous proven or probable IFI from the start of voriconazole prophylaxis until the 12-month Follow-up Visit.

Secondary Objectives:

- To evaluate the efficacy of voriconazole as secondary prophylaxis on the rate of occurrence of proven and probable IFI from the start of voriconazole prophylaxis until the 6-month Follow-up Visit
- To evaluate the efficacy of voriconazole as secondary prophylaxis on the rate of occurrence of proven and probable IFI from the start of voriconazole prophylaxis until the End of Prophylaxis (EOP) Visit
- To evaluate time to occurrence of proven/probable recurrent (same pathogen as previous IFI) IFIs from the start of voriconazole prophylaxis
- To evaluate time to occurrence of proven/probable new (new pathogen) IFIs from the start of voriconazole prophylaxis

- To evaluate the proportion of subjects experiencing proven/probable recurrent/new IFIs from the start of voriconazole prophylaxis until 12 months after transplant

- To evaluate the proportion of subjects who survived free of IFI at 6 and 12 months after transplant

- To evaluate the safety and tolerability of voriconazole as secondary prophylaxis after allogeneic SCT.

METHODS

Study Design: This was a Phase 3, 12-month, prospective, non-comparative, open-label, international, multicenter study of voriconazole as secondary prophylaxis for IFI in subjects undergoing SCT. This study had 3 phases: screening, prophylaxis, and follow-up. Subjects meeting inclusion and exclusion criteria started prophylaxis treatment at least 48 hours after the end of chemotherapy. After EOP, follow-up visits were scheduled for 6 and 12 months after transplantation. The maximum exposure to the study drug for an individual subject was planned to be 153 days. The maximum time in the study, including follow-up, was planned to be 12 months.

The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Procedures	**Screening**	**Prophylaxis**						
Study Day	**Day -5 to -2**	**Begin of Prophylaxis Day -3 to 0[a]**	**Day -2 to +1**	**Baseline Transplant Day 0**	**Day 14-42 Bi-Weekly; Day 70-126 4-Weekly[b]**	**EOP[b]**	**FU 6**	**FU 12**
Visit Number	**1**	**2**	**3**		**4-6[c] 7-9[c]**	**10[c]**	**11[d]**	**12[d]**
Screen evaluation Obtain written informed consent	X							
Pregnancy test	X							
Demographic data	X							
Height	X							
Medical history/ drug allergies	X							
Primary diagnosis and status at transplant	X							
History of previous (within last 6 months) IFI	X							
Test for candiduria	X							
Eligibility (inclusion/exclusion criteria)	X	X						
Safety Physical exam	X	X	X		X	X	X	X
ECG	X		X[e]		X[e]	X		
Clinical signs and symptoms of fungal disease		X	X		X	X	X	X
Check for GvHD					X	X	X	X
Weight	X	X	X		X	X		
Body temperature	X	X	X		X	X	X	X
Imaging tests (if applicable)[f]	X[f]	X[f]	X[f]		X[f]	X[f]	X[f]	X[f]
Culture[g]	X	X	X		X	X	X	X
Serum galactomnnan antigen[h]	X				X	X	X[f]	X[f]
Hematology	X	X	X		X	X		
Biochemistry	X	X	X		X	X		
Concomitant medications/ elective surgeries/procedures	X	X	X		X	X	X[i]	X[i]
Concomitant nondrug treatment	X	X	X		X	X		

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Procedures	**Screening**	**Prophylaxis**						
Study Day	**Day -5 to -2**	**Begin of Prophylaxis Day -3 to 0[a]**	**Day -2 to +1**	**Baseline Transplant Day 0**	**Day 14-42 Bi-Weekly; Day 70-126 4-Weekly[b]**	**EOP[b]**	**FU 6**	**FU 12**
Visit Number	**1**	**2**	**3**		**4-6[c] 7-9[c]**	**10[c]**	**11[d]**	**12[d]**
Adverse events	X[j]	X	X		X	X	X	X
Study prophylaxis Study drug dispensed		X	X		X			
Study drug record and accountability		X	X		X	X		
Study drug labels		X	X		X	X		
Miscellaneous schedule next visit	X	X	X		X	X	X	
End of chemotherapy/and radiation	X							
Stem cell transplantation				X				

AEM = adverse event monitoring; ATG = antithymocyte globulin; ECG = electrocardiogram; EOP = end of prophylaxis; FU = follow up; GvHD; = graft versus host disease; IFI = invasive fungal infection; QTc = corrected QT interval; PMN = polymorphonuclear; QTc = corrected QT interval.

a. 48 hours after end of chemotherapy.
b. 100 days or ≤150 days after transplant in any of the following clinical situations.
c. Only serious adverse events need to be reported (on AEM form).
d. Visit window: ±2 days.
e. Visit window: ±4 days in case of an increase of the QTc to >500 msec or if there is a change from Baseline of >60 msec, the subject had to be discontinued from voriconazole prophylaxis.
f. Subject was receiving prednisone (≥0.2 mg/kg), OKT3, or mycophenolate mofetil.
g. Subject was receiving ATG or had received ATG within the 4 weeks prior to Day 100.
h. Subject was neutropenic (PMN <500/mm^3) or had been neutropenic within the 10 days prior to Day 100 whenever applicable at Screening and then whenever fungal infection suspected. It was continued as long as positive.
i. Only systemic antifungals.
j. At Screening (to exclude possible hidden aspergillosis), then 2 times per week for the first 21 days, 1 time per week from Day 22 until Day 60 and, for subjects with GvHD or on steroids, every 2 weeks from Day 61 after day of transplant until the EOP.

Number of Subjects (Planned and Analyzed): The study planned to enroll 70 subjects. A total of 46 subjects (1 in Portugal, 9 in Spain, 11 each in France and Germany, 2 each in Switzerland and Sweden, 4 in Belgium, and 6 in the UK) were screened for inclusion, 45 of whom fulfilled all study inclusion/exclusion criteria and were randomized to treatment.

Since it proved difficult to find a sufficient number of suitable subjects to enroll into the study within the planned timelines, the decision was made not to extend the period of recruitment to achieve the target of 63 subjects. The reduction of sample size to 45 treated subjects was acceptable since the original target was based on anticipated recruitment rate and not on any formal statistical hypotheses.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 18 years and older with proven or probable IFI in previous 12 months receiving an allogeneic SCT for any hematological disease. Females of childbearing potential had to have a negative serum β-human chorionic gonadotropin pregnancy test and be practicing an effective form of contraception.

Excluded were subjects who had severe disease other than the underlying condition, active, symptomatic uncontrolled invasive fungal infection, any evidence of active fungal disease as defined by Mycoses study group – European organization for research and treatment of cancer (MSG-EORTC) criteria concomitant use of voriconazole 36 hours before chemotherapy until 48 hours after chemotherapy and other medical conditions, including human immunodeficiency virus infection positive serology that interfered with the evaluation of therapeutic response or safety of study drug.

Study Treatment: All subjects received voriconazole as study medication for prophylaxis. The intravenous (IV) loading dose was 6 mg/kg every 12 hours (q12h) for 2 doses, followed by maintenance doses of 4 mg/kg IV q12h. The oral loading dose was 400 mg q12h for 2 doses, followed by maintenance doses of 200 mg q12h, if the subject weighed ≥40 kg. If the subject weighed <40 kg, the oral loading dose was 200 mg q12h for 2 doses, followed by maintenance doses of 100 mg q12h.

Voriconazole prophylaxis was administered for a minimum of 100 days after transplant and was extended for up to an additional 50 days in any of the following clinical situations:

- Subject was receiving prednisone (≥0.2 mg/kg), muromonab (OKT3), or mycophenolate mofetil
- Subject was receiving antithymocyte globulin (ATG) or had received ATG within the 4 weeks before Day 100
- Subject was neutropenic (polymorphonuclear neutrophil leukocytes <500/mm^3) or had been neutropenic within the 10 days before Day 100.

Depending on the subject's status, voriconazole could have been switched between the oral tablet formulation and IV formulation after the loading dose was completed. Use of either IV or oral treatment was left to the discretion of the Investigator.

Efficacy Endpoints:

Primary Endpoint:

- The rate of proven or probable IFIs between the start of voriconazole prophylaxis and the 12 months follow-up, defined according to the EORTC-MSG Criteria

Secondary Endpoints:

- The rate of proven or probable IFIs at the 6-months Follow-up Visit
- The rate of proven or probable IFIs at the EOP
- The time to occurrence of proven/probable recurrent (same pathogen as previous IFI) IFI from the start of voriconazole prophylaxis
- The time to occurrence of proven/probable new (new pathogen) IFIs from the start of voriconazole prophylaxis
- The proportion of subjects experiencing proven/probable recurrent/ new IFIs from the start of voriconazole prophylaxis until 12 months after transplant
- The proportion of subjects who survive free of IFI at the 6 and 12-months following transplant
- The safety and tolerability of voriconazole

Safety Evaluations: Subjects were evaluated for adverse events (AEs), clinical laboratory values, vital signs measurements, and electrocardiogram (ECG) results.

Statistical Methods:

The following populations were used for analysis:

- Intent- to-Treat Population: All subjects who had taken at least one dose of study medication and have at least one post-enrollment (Visit 2) efficacy assessment.
- Modified Intend-to-Treat Population (MITT): Subjects were eligible for inclusion in the modified intent-to-treat group and considered evaluable for efficacy if they are a member of the intent-to-treat (ITT) population and in addition have a prior diagnosis of proven or probable IFI, confirmed by the Data Review Committee according to the definitions of the inclusion criteria.
- Per Protocol Population: Subjects were eligible for inclusion in the per protocol population if they fulfilled the criteria of MITT population and did not present any major protocol violation.

- Safety Population: All subjects who received at least one dose of treatment were considered in the safety analysis.

Since this was an open-label, non-comparative study design, there were no formal hypotheses defined for this study. The primary efficacy analysis was based on the MITT population and the primary endpoint of the proportion of subjects developing a proven or probable IFI between start of prophylaxis and the 12-month follow-up visit. These data were summarized using both the number and percentage of successes. An exact 95% confidence interval (CI) was provided for each percentage. Supporting analyses were also presented based on the per protocol population and the ITT population. The secondary analyses were conducted for the MITT population. The safety analyses included all subjects who received at least 1 dose of study medication.

RESULTS

Subject Disposition and Demography: A total of 46 subjects were screened for inclusion, 45 of whom passed screening and were assigned to treatment (Table 2). A total of 16 subjects were discontinued from the study (failed to reach the 12-month follow-up visit), including 11 subjects who discontinued due to death. Two (2) additional deaths were reported: 1 subject was discontinued (lost to follow-up) and then died prior to Month 12, and 1 subject completed the study and died after Month 12.

Two subjects from 1 site were excluded from the analyses of all efficacy endpoints; however, all subjects were included in the safety analyses.

Table 2. Subject Disposition

Disposition	Voriconazole Number of Subjects
Screened	46[a]
Assigned to treatment	45
Treated	45
Completed study (up to Visit/Month 12)[b,c]	29
Discontinued (before Visit/Month 12) from safety population	16
Subject died	11
Adverse event	2
Lost to follow-up[d]	1
Other	1
No longer willing to participate	1
Analysis Sets	
Safety	45
ITT[e]	43
MITT[e]	40
PP[e]	32

Visit 12 is the 12-month follow-up visit.
ITT = intent-to-treat; MITT = modified intent-to-treat; PP = per protocol.
a. Note that this was the number of subjects with data at Screening in the study database. It was possible that other subjects were screened; sometimes screen failures do not get added into the database.
b. Included 2 subjects from a site who were evaluated for safety but not for efficacy.
c. One (1) subject completed the study and died after Month 12.
d. One (1) subject was discontinued (lost to follow-up) and then died prior to Month 12.
e. In addition, the 2 subjects from the excluded United Kingdom site were omitted from the efficacy analyses.

Demographic characteristics in the safety population are summarized in Table 3. More than half of the subjects treated were male and the mean age of all subjects was approximately 48 years (range 22 to 72 years).

Table 3. Subject Demographics (Safety Population)

Demographics	Voriconazole N=45
Sex (number of subjects)	
Male	28
Female	17
Age (years)	
Mean (SD)	48.4 (14.1)
Range	22-72
Body mass index	
Mean (SD)	24.6 (4.0)
Range	18.1-35.5

N = number of subjects; SD = standard deviation.

Efficacy Results: The proportion of subjects developing a proven or probable IFI from the start of prophylaxis until the 12-month follow-up visit is presented in Table 4. All subjects in the MITT population were required to have a Data Review Committee-confirmed diagnosis of previous proven or probable IFI, the most frequently observed was probable aspergillosis (approximately 60% of subjects).

Table 4. Proportion of Subjects Developing a Proven or Probable IFI From Start of Prophylaxis Until 12-Month Follow-Up Visit (MITT Population)

Voriconazole N=40	Number of Evaluable Subjects	Number (%) of Subjects With Proven Or Probable IFI	95% CI[a]
Proven or probable IFI	28	3 (10.7)	(0.02, 0.28)

N is the number of subjects in the MITT population.
A subject is only included in the percentage if they either developed an IFI by the 12-Month Follow-up Visit or provided an assessment of IFI at the 12-Month Follow-up Visit.
CI = confidence interval; IFI = invasive fungal infection; MITT = modified intent-to-treat; N = the number of subjects in the MITT population.
a. Exact 95% CI for proportion.

The proportion of subjects developing a proven or probable IFI from the start of prophylaxis until the 6-Month Follow-up Visit is presented in Table 5.

These results (MITT population) show that the 3 proven or probable IFIs noted above (Table 4) all occurred within the first 6 months of treatment and that the IFI rate was low (9.4%) among the 32 evaluable subjects.

Table 5. Proportion of Subjects Developing a Proven or Probable IFI from Start of Prophylaxis until 6-Month Follow-Up Visit (MITT Population)

Voriconazole N=40	Number of Evaluable Subjects	Number (%) of Subjects With Proven Or Probable IFI	95% CI[a]
Proven or probable IFI	32	3 (9.4)	(0.02, 0.25)

N is the number of subjects in the MITT population.
A subject is only included in the percentage if they either developed an IFI by the 6-Month Follow-up Visit or provided an assessment of IFI at the 6 Month Follow-up Visit.
The denominator for the percentage is the count of evaluable subjects.
CI = confidence interval; IFI = invasive fungal infection; MITT = modified intent-to-treat; N = the number of subjects in the MITT population.
a. Exact 95% CI for proportion.

The proportion of subjects developing a proven or probable IFI from the start of prophylaxis until EOP is summarized in Table 6.

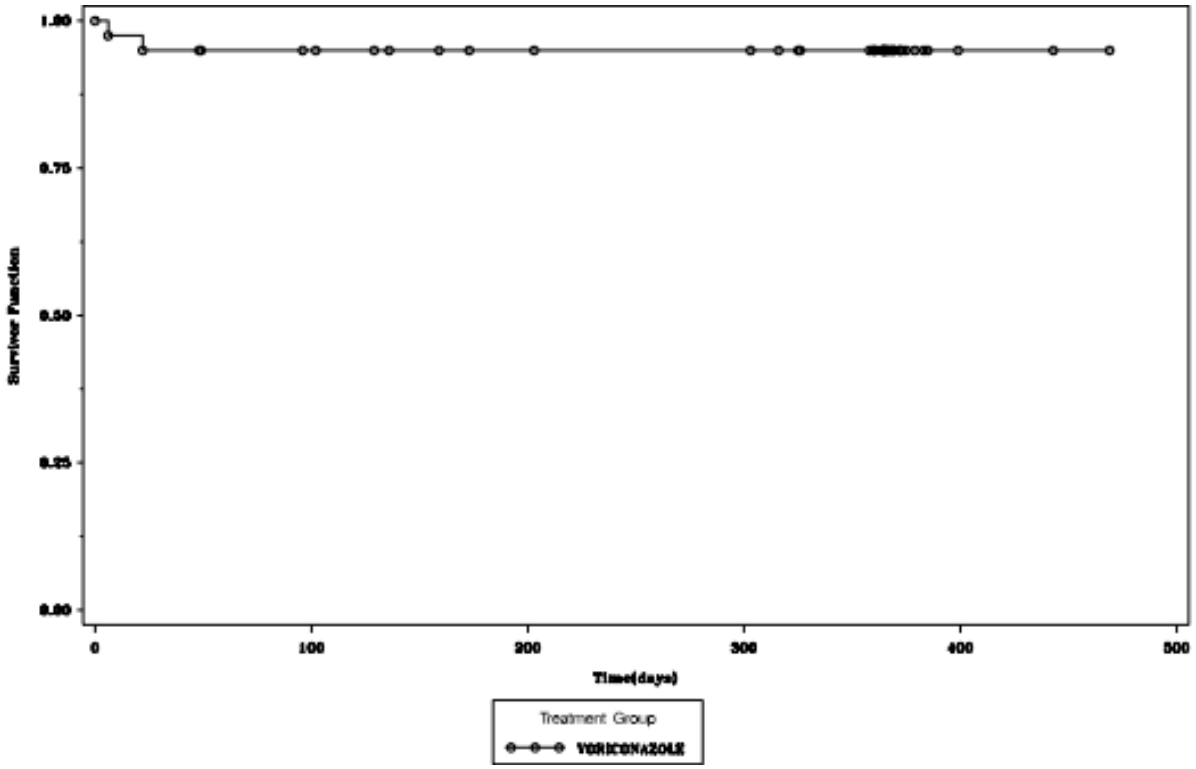
Table 6. Proportion of Subjects Developing a Proven or Probable IFI From Start of Prophylaxis Until End of Prophylaxis (MITT Population)

Voriconazole N=40	Number of Evaluable Subjects	Number (%) of Subjects With Proven or Probable IFI	95% CI[a]
Proven or probable IFI	32	3 (9.38)	(0.02, 0.25)

A subject is only included in the percentage if they either developed an IFI by the EOP visit or provided an assessment of IFI at the EOP Visit.
The denominator for the percentage is the count of evaluable subjects.
CI = confidence interval; IFI = invasive fungal infection; MITT = modified intent-to-treat; N = the number of subjects in the MITT population.
a. Exact 95% CI for proportion.

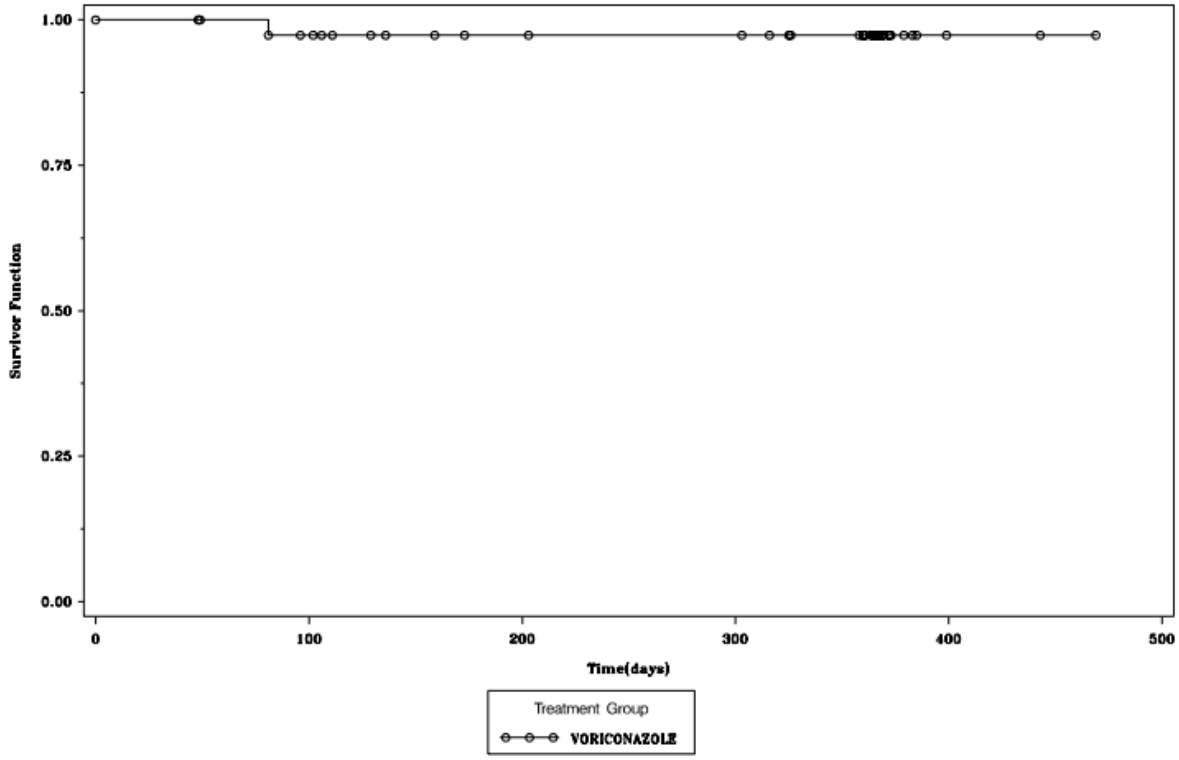
Figure 1 presents the time (in days) to the occurrence of a proven or probable recurrent IFI from the start of prophylaxis and Figure 2 presents the time (in days) to the occurrence of a proven or probable new IFI from the start of prophylaxis. Note that the time of IFI in each of these figures corresponds to the day of that IFI, where Day 1 is the day of the start of prophylaxis. In addition, the day of occurrence of the IFI is that recorded in the assessment of IFI according to EORTC/MSG criteria data. In each case, this date of IFI is later than that recorded in the mycology culture data.

Figure 1. Time to Occurrence of Proven/Probable Recurrent (Same Pathogen as Previous IFI) IFI From the Start of Voriconazole Prophylaxis



IFIs = invasive fungal infection.

Figure 2. Time to Occurrence of Proven/Probable New (New Pathogen) IFIs From the Start of Voriconazole Prophylaxis



IFIs = invasive fungal infection.

Table 7 presents for the MITT population, 76% of subjects survived until the 6-Month Follow-up Visit without a proven or probable IFI.

Table 7. Proportion of Subjects Who Survived Free of Proven or Probable IFI at 6-Month Follow-Up Visit (MITT Population)

Voriconazole N=40	Number of Evaluable Subjects	Number (%) of Subjects WHO Survive Free of Proven or Probable IFI	95% CI[a]
Proven or probable IFI	38	29 (76.32)	(0.60, 0.89)

N is the number of subjects in the MITT Population.
A subject is excluded from the percentage if they failed to provide an assessment of IFI at the 6-Month Follow-up Visit (unless they died before that visit or experienced an IFI before that visit).
The denominator for the percentage is the count of evaluable subjects.
CI = confidence interval; IFI = invasive fungal infection; MITT = modified intent-to-treat.
a. Exact 95% CI for proportion.

At the 12-Month Follow-up Visit, the proportion without a proven or probable IFI was 66% (Table 8).

Table 8. Proportion of Subjects Who Survived Free of Proven or Probable IFI at 12-Month Follow-Up Visit (MITT Population)

Voriconazole N=42	Number of Evaluable Subjects	Number (%) of Subjects Who Survive Free of Proven Or Probable IFI	95% CI[a]
Proven or probable IFI	38	25 (65.79)	(0.49, 0.80)

N is the number of subjects in the MITT population.
A subject is excluded from the percentage if they failed to provide an assessment of IFI at the 12-Month Follow-up Visit (unless they died before that visit or experienced an IFI before that visit).
The denominator for the percentage is the count of evaluable subjects.
CI = confidence interval; IFI = invasive fungal infection; MITT = modified intent-to-treat; N = the number of subjects in the MITT population.
a. Exact 95% CI for proportion.

No pharmacokinetic or pharmacodynamic evaluations were performed in this study.

Safety Results:

Table 9 presents the incidence of treatment-emergent AEs (TEAEs) reported for ≥5 subjects. The most common TEAEs (all causality) were mucosal inflammation, diarrhea, vomiting, pyrexia, headache and graft versus host disease.

Table 9. Incidence of TEAEs (Reported for ≥5 Subjects) (All Causalities)

MedDRA (v11.0) Preferred Term	Voriconazole N=45
Mucosal inflammation	17
Diarrhoea	16
Vomiting	16
Pyrexia	15
Headache	14
Graft versus host disease	13
Hypertension	9
Abdominal pain	8
Febrile neutropenia	8
Thrombocytopenia	8
Anaemia	7
Insomnia	7
Abdominal pain upper	6
Nausea	6
Erythema	5
Rash	6
Constipation	5
Chills	5
Oedema peripheral	5
Hepatotoxicity	5
Cytomegalovirus infection	5

Subjects are counted only once per treatment in each row. For the TESS algorithm any missing severities have been 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 is summarized. Missing baseline severities are imputed as mild.
Includes data up to 7 days after last dose of study drug.
MedDRA (v11.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects;
TEAEs = treatment-emergent adverse events; TESS = treatment-emergent signs and symptoms;
v = version.

The majority of AEs in this study were not considered by the Investigator to be treatment-related; 59 TEAEs (Table 10) were reported for 26 subjects. Most treatment-related AEs were mild or moderate in intensity. The most common treatment-related were hepatotoxicity (4 subjects), hallucination (3 subjects), and headache (3 subjects).

Table 10. Incidence of Treatment-Emergent Adverse Events (Reported for ≥2 Subjects) (Treatment-Related)

MedDRA (v11.0) Preferred Term	Voriconazole (N=45)
Visual disturbance	2
Vomiting	2
Asthenia	2
Cholestasis	2
Cytolytic hepatitis	2
Hepatotoxicity	4
Liver function test abnormal	2
Headache	3
Loss of consciousness	2
Hallucination	3
Hyperhidrosis	2
Hypertension	2

Subjects are counted only once per treatment in each row. For the TESS algorithm any missing severities have been 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 is summarized. Missing baseline severities are imputed as mild.
Includes data up to 7 days after last dose of study drug.
MedDRA (v11.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects;
TESS = treatment-emergent signs and symptoms; v = version.
a. 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 is taken.

A total of 23 subjects experienced 52 treatment-emergent SAEs during this study. A total of 9 subjects experienced 15 treatment-emergent SAEs that were considered to be related to voriconazole, the most frequently reported being hepatotoxicity (in 2 subjects) (Table 11).

Table 11. Treatment-Emergent, Treatment-Related Serious Adverse Events, by Subject (Safety Population)

Serial Number	Treatment Phase	Start Day / Stop Day	SAE	Study Drug Action Taken	Outcome
1[a]	Active	42/>49	Hepatotoxicity	None	Still present
2[a]	Active	8/15	Cholestasis[b]	Permanent DC of drug	Resolved
	Post	1/8	Cholestasis[b]	Permanent DC of drug	Resolved
3[a]	Active	35/37	Headache	None	Resolved
	Active	35/39	Hypertension	None	Resolved
	Active	35/35	Loss of consciousness	None	Resolved
4	Active	71/78	Hepatomegaly[b]	None	Resolved
	Post	1/6	Hepatomegaly[b]	None	Resolved
	Active	70/78	Liver function test abnormal[b,c]	Permanent DC of drug	Resolved
	Post	1/6	Liver function test abnormal[b]	Permanent DC of drug	Resolved
5[a]	Active	78/88	Sputum culture positive[b]	Permanent DC of drug	Resolved
	Post	1/24	Sputum culture positive[b]	Permanent DC of drug	Resolved
6	Active	11/22	Venoocclusive disease[b]	Permanent DC of drug	Resolved
	Post	1/23	Venoocclusive disease[b]	Permanent DC of drug	Resolved
7	Active	38/45	Hepatotoxicity[b,c]	Permanent DC of drug	Resolved
	Post	1/59	Hepatotoxicity[b]	Permanent DC of drug	Resolved
8	Active	28/39	Diarrhoea	None	Resolved
	Active	28/65	Erythema	None	Resolved
	Active	28/36	Vomiting	None	Resolved
	Active	72/79	Hepatitis toxic[b]	Permanent DC of drug	Resolved
	Post	1/16	Hepatitis toxic[b]	Permanent DC of drug	Resolved
9	Active	9/13	Hallucination	Permanent DC of drug	Resolved

DC = discontinuation; F = female; M = male; SAE = serious adverse event.
a. Subject died.
b. This event began during treatment and ended after treatment had stopped; it is listed twice to account for both the Active and Post treatment phases but is counted as the same single adverse event.
c. Subject discontinued the study due to this adverse event.

Two subjects discontinued the study due to AEs: 1 subject due to an AE and an SAE of liver function test abnormal and another subject with an SAE of hepatotoxicity. Both of these events resolved and both were considered by the Investigators as being treatment-related.

A total of 13 subjects died. Eleven (11) subjects (24%) died during study participation between 48 and 326 days after start of prophylaxis. In addition, 1 subject was withdrawn from the study (lost to follow-up) and then died prior to Month 12, and other subject died beyond 1 year after completing the study (Table 12). All deaths were due to causes unrelated to study medication. Causes of death included relapse of leukemia (5 subjects), respiratory failure or pneumopathy of unknown origin (3 subjects), GvHD (2 subjects), scedosporiosis in the setting of leukemia relapse (1 subject) and sepsis (1 subject). Two causes of death (GvHD and sepsis) were reported for the remaining subject.

Table 12. Deaths (Safety Population)

Serial Number	Date of First Dose	Date of Death	Study Day of Death	Cause of Death
1	27-Feb-07	12-Jul-07	136	Relapse of acute leukaemia
2	6-Mar-07	12-May-07	68[a]	Disease progression
3	11-May-05	31-Mar-06	325	Relapse AML
4	23-Feb-07	1-Jul-07	129	Acute pulmonary edema
5	30-Mar-07	13-Jul-07	106	Scedosporium prolificans infection
6	26-Sep-06	3-Mar-07	159	GvHD
7	5-May-06	26-Mar-07	326	Extensive pulmonary chronic GvHD
8	25-Jul-06	12-Feb-07	203	Suspected pneumopathy
9	2-Apr-07	6-Jul-07	96	Sepsis
10	25-Oct-05	2-Feb-07	466[b]	GvHD and sepsis
11	21-Mar-07	9-Jul-07	111	Leukemia
12	9-Sep-05	26-Oct-05	48	Leukemia relapse
13	5-Dec-06	3-Oct-07	303	Respiratory failure

Causality was assessed by the Investigator as unrelated to study drug.
AML = acute myeloid leukemia; GvHD = graft versus host disease.
a. Subject was withdrawn from the study (lost to follow-up) and then died.
b. Subject completed the study and then died.

The most common clinical laboratory abnormalities without regard to baseline abnormality, occurring in ≥33% of subjects, were associated with hematology parameters (platelets, white blood cells count, and absolute lymphocytes and total neutrophils), liver function test parameters (direct bilirubin and alanine transaminase [ALT]), and the electrolyte magnesium. Notable median increases from Baseline were observed for hematology parameters (WBC count, lymphocytes, and monocytes), liver function test parameters (direct bilirubin, aspartate aminotransferase ALT, and alkaline phosphatase) and the renal parameter blood urea nitrogen.

A total of 39 subjects had at least 1 ECG recording, 10 of whom had 1 or more ECGs outside normal limits (mostly tachycardia and/or bradycardia). No clinically important treatment-related changes in vital signs measurements were observed.

CONCLUSIONS:

- The primary objective was assessment of the rate of proven or probable IFI in subjects with previous history of IFI undergoing allogeneic SCT, and receiving voriconazole as secondary prophylaxis. Subjects in this study had a 10.7% IFI rate evaluated using a complete case analysis (3 occurrences among 28 subjects in the MITT population who either developed an IFI by Month 12, or provided an assessment of IFI at the 12-Month Follow-up Visit).

- In comparison, the crude incidence rate of IFI in the MITT population was 7.5% (3 occurrences among the 40 subjects of the MITT population).

- All 3 of the incidences of IFI occurred during the first 6 months of treatment.

- Secondary efficacy results (based on other populations and at other time points and all using a complete case analysis), provided an overall IFI rate ranging from 9.4% to 13.0%.

- Voriconazole was well tolerated in this population composed primarily of subjects with myeloid leukemia. A total of 12 subjects died prior to the 12-Month Follow-up Visit and 1 additional death was reported after Month 12. No death was related to treatment, all were attributed (either directly or indirectly) to the subject's underlying condition.

- A total of 9 subjects experienced treatment-emergent SAEs that were considered to be related to voriconazole, the most frequently reported being hepatotoxicity (in 2 subjects). The most frequently reported AEs were mucosal inflammation, diarrhea, vomiting, pyrexia, headache and graft versus host disease, and were generally attributed to the subjects' other medical conditions or to concomitant medications. Most treatment-related AEs were mild or moderate in intensity. The most common treatment-related AEs were hepatotoxicity (4 subjects), hallucination (3 subjects), and headache (3 subjects). Two subjects reported 3 treatment-related AEs of the eye disorders system organ class. One (1) subject experienced both visual disturbance and chromatopsia, the other experienced visual disturbance only. All 3 events were mild in severity, nonserious, and resolved without sequelae.

- Two subjects discontinued the study due to AEs (hepatotoxicity and liver function test abnormal in 1 subject each), both of which were serious and considered to be related to treatment. Nineteen (19) additional subjects permanently discontinued study medication due to AEs but were not discontinued from the study; AEs in 12 of these subjects were considered treatment-related. Of these 19 subjects, a total of 10 permanently discontinued study medication due to hepatic events, 8 of which were considered treatment-related.