

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med* 2007;356:335-47.

## Supplementary Appendix

Supplement to: Ullmann, AJ, Lipton, JH, Vesole, DH, et al. Posaconazole vs. fluconazole for prophylaxis of invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients with severe graft-versus-host disease

### METHODS:

#### Details on the Inclusion criteria:

- Male or female subjects were to be 13 years or greater, weighing >34 kg, any race.
- Hematopoietic progenitor cell transplant subjects with the following risk factors for invasive fungal infections; may have fulfilled either (1), OR (2) [a or b] below:
  - (1) Grade 2-4 acute GVHD<sup>23, 24</sup> being treated with high dose immunosuppressive therapy requiring the addition or substitution of one of the following to the subject's prior immunosuppressive regimen:
    - a) at least 1 mg per kg per day of methylprednisolone or equivalent,
    - b) antithymocyte globulin (ATG) for the therapy of acute GVHD,
    - c) tacrolimus, mycophenolate mofetil, or other steroid-sparing immunosuppressive regimen
  - OR
  - (2) Chronic GVHD<sup>23, 24</sup> being treated with high dose immunosuppressive therapy requiring the addition or substitution of at least one of the following to the subject's prior immunosuppressive regimen:
    - (a) at least 1 mg per kg of prednisone (0.8 mg per kg methylprednisolone or equivalent), every second day,
    - (b) the addition of one or more immunosuppressive therapies to the subject's prior

maintenance regimen so that the subject is on at least two therapies for the treatment of chronic extensive GVHD (such therapies may include tacrolimus, mycophenolate mofetil, PUVA therapy, radiation therapy, or photopheresis)

- (3) Subjects must meet the clinical criteria of Grade 2-4 acute GVHD or chronic GVHD at the time of randomization, or be likely to continue on high dose immunosuppressive therapy as outlined in items 1 or 2 above for management of GVHD for more than 2 weeks.

Classification of subjects into acute or chronic GVHD should be made on the basis of the clinico-pathologic characteristics of the GVHD, rather than on the interval of time between the transplant and onset or exacerbation of the GVHD. If a subject has features of both acute and chronic GVHD, that subject's GVHD classification should be made based on the dominant clinico-pathologic characteristics.

Subjects can be randomized while on antifungal prophylaxis as long as that prophylaxis is discontinued prior to the start of study drug.

Subject (parent or legal guardian for minor) must be willing to give written informed consent.

Subjects must be able to adhere to dosing, mandatory procedures and visit schedules.

Subjects must be able to take study medication (suspension and capsules) orally.

Females of childbearing potential must use a reliable barrier-type method of contraception. For subjects taking oral contraceptives, an additional reliable barrier-type method must have been used during this study.

Females of childbearing potential must have a negative serum pregnancy test at Baseline or within 72 hours prior to start of study drug.

**Details on the Exclusion criteria:**

- History of proven or probable mould infection requiring secondary prophylaxis.
- Subjects who are suspected of having an invasive fungal infection, excluding *Pneumocystis pneumonia*.
- Use of medications that are known to interact with azoles and that may lead to life-threatening side effects<sup>25</sup>: terfenadine, cisapride, ebastine at entry or within 24 hours prior to entry; or astemizole at entry or within 10 days prior to entry.
- Use of medications that are known to lower the serum concentration/efficacy of azole antifungals: rifampin, carbamazepine, phenytoin, rifabutin, barbiturates, isoniazid at entry or within 1 week prior to entry.
- Subjects receiving vinca alkaloids or anthracyclines at entry.
- Subjects with an ECG with a prolonged QTc interval by manual reading: QTc >450 msec for males and QTc >470 msec for females.
- Any condition requiring the use of prohibited drugs.
- Neurologic disorder or impairment expected to be progressive.
- Subjects whose laboratory results indicated one of the following:
  - Hepatic function studies: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >10 times upper limit of normal.
  - Estimated creatinine clearance <20 mL/minute or subjects requiring dialysis.
  - Prior enrollment in this study.
  - Women who are pregnant or nursing.
  - History of hypersensitivity or idiosyncratic reactions to azole drugs.

- Investigational (new chemical entity) drug use in the 30 days prior to enrollment.
- Subjects with a high probability of death within 7 days of enrollment.
- Subjects who in the opinion of the investigator had clinical conditions which may have made evaluation of the safety and efficacy of this drug difficult.

**Definition of probable or proven invasive fungal infections:**

Proven and probable invasive fungal infections (IFI) were defined as described in Ascigliu et al., CID 2002, 34:7-14. Briefly, a proven IFI was defined as a deep tissue infection with histopathologic evidence or a positive culture result from a normally sterile site. Diagnosis of a probable IFI was made in patients with at least 1 host factor criterion, 1 microbiologic criterion, and 1 major (or 2 minor) clinical criteria.

***Proven invasive fungal infection:***

Histo/cytopathology showing hyphae or spherule (filamentous fungi without yeast forms) from needle aspiration or biopsy with evidence of associated tissue damage (either microscopically or unequivocally by imaging); or positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection

***or***

Histo/cytopathology showing yeast cells and/or pseudohyphae from a needle aspiration or biopsy, excluding mucous membranes

***or***

Positive culture obtained by a sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine, sinuses, and mucous membranes

***or***

Microscopy (India ink, mucicarmine stain) or antigen positivity for *Cryptococcus* species in cerebrospinal fluid

***Probable invasive fungal infection:***

Meets at least one host, microbiologic, and clinical criterion

*Host Criteria:*

- Neutropenia (<500 neutrophils/mm<sup>3</sup> for >10 days)
- Persistent fever for >96 h refractory to appropriate, broad-spectrum antibacterial treatment
- Body temperature either >38°C or <36°C and any of the following predisposing conditions:
  - a) Prolonged neutropenia (>10 days) in previous 60 days,
  - b) Recent (previous 30 days) or current use of significant immunosuppressive agents,
  - c) IFI in a previous episode
  - d) Coexistence of symptomatic AIDS
- Signs and symptoms indicating graft-versus-host disease
- Prolonged (>3 weeks) use of corticosteroids

*Microbiologic data:*

- Positive culture of a mould (including *Aspergillus* spp., *Fusarium* spp., Zygomycetes, or *Scedosporium* spp.) or *Cryptococcus neoformans* from sputum or bronchoalveolar lavage
- Positive culture or cytologic/direct microscopic evaluation for mould from sinus aspirate
- Positive cytologic/direct microscopic evaluation for mould or *Cryptococcus* species from sputum or bronchoalveolar lavage

- Positive result for *Aspergillus* antigen in bronchoalveolar lavage fluid, CSF, or  $\geq 2$  blood samples
- Positive result for cryptococcal antigen in blood sample
- Positive cytology or direct microscopy examination for fungal elements other than *Cryptococcus* in sterile body fluids
- Two positive urine cultures of yeasts in the absence of urinary catheter
- Two positive results for *Aspergillus* antigen in serum
- Positive result of blood culture for *Candida* spp.

*Clinical Criteria:*

Signs of infection:

- Lower respiratory tract infection
- Sinonasal infection
- CNS infection
- Disseminated fungal infection
- Chronic disseminated candidiasis
- Candidemia

**Definition of Resistance:**

Fluconazole interpretive breakpoints for minimum inhibitory concentrations (MICs) determined by the Clinical Laboratory Standards Institute (CLSI; formerly known as the National Committee for Clinical Laboratory Standards) M27-T broth macrodilution methodology are: isolates for which MICs are  $\leq 8$   $\mu\text{g/mL}$  were considered susceptible to fluconazole, isolates with MICs of

$\geq 16-32 \mu\text{g/mL}$  were considered susceptible but dose dependent (S-DD), isolates with MICs of  $\geq 64 \mu\text{g/mL}$  were considered resistant.

MIC breakpoints for itraconazole apply only to mucosal candidal infections and are as follows: susceptible,  $\leq 0.125 \mu\text{g/mL}$ ; S-DD,  $0.25-0.5 \mu\text{g/mL}$ ; and resistant,  $\geq 1.0 \mu\text{g/mL}$ .

### **Time period definitions for this trial:**

#### **Observation Period (Any Time):**

Interval of time from randomization through last contact

#### **Fixed Treatment Period (Primary Time Period; fixed time period):**

Interval of time which begins on the randomization date and ends on day 112

#### **Exposure Period (While on Treatment):**

Interval of time which begins on the first day of treatment and ends on the last day of treatment plus 7 days

### **Assessment of Noninferiority:**

Posaconazole will be considered to be at least noninferior to fluconazole, with respect to the primary efficacy endpoint based on all treated patients, if the upper limit of the 95% confidence interval for the odds ratio does not exceed a maximum value corresponding to a percentage difference in incidence rates (with respect to the incidence rate of fluconazole) of 15%. The maximum value will be computed as follows:

Let

$\tilde{\pi}_{POS}$  = *Posaconazole incidence rate to be ruled out,*

$\tilde{\pi}_{FLZ}$  = *Fluconazole incidence rate to be ruled out,*

$\hat{\pi}$  = **Estimated overall incidence rate (total number of events/total number of patients),**

$N_{POS}$  = **Number of patients in the posaconazole treatment group,**

$N_{FLZ}$  = **Number of patients in the fluconazole treatment group.**

Then solve the following two equations for  $\tilde{\pi}_{POS}$  and  $\tilde{\pi}_{FLZ}$  :

$$\frac{N_{POS}\tilde{\pi}_{POS} + N_{FLZ}\tilde{\pi}_{FLZ}}{N_{POS} + N_{FLZ}} = \hat{\pi}$$

$$\frac{\tilde{\pi}_{POS} - \tilde{\pi}_{FLZ}}{\tilde{\pi}_{FLZ}} = 0.15$$

Then calculate the maximum value for the upper confidence limit of the odds ratio as:

$$\text{Maximum Value} = \frac{\tilde{\pi}_{POS}(1 - \tilde{\pi}_{FLZ})}{\tilde{\pi}_{FLZ}(1 - \tilde{\pi}_{POS})}$$

If the upper confidence limit of the 95.01% confidence interval for the observed odds ratio was less than the maximum value specified above, the non-inferiority would be declared. At the time of the final analysis, this maximum value specified above was 1.16, and the observed upper confidence limit of the odds ratio of posaconazole vs. comparator was 1.07. Since the observed upper limit was less than the maximum value, non-inferiority was declared.

## RESULTS:

**TABLE A: Patient Demographics, Baseline Disease Characteristics, and Invasive Fungal Infection Risk Factors at Baseline**

	Fixed Treatment Period (Primary Time Period/ITT)		
	Posaconazole (n=301)	Fluconazole (n=299)	<i>P</i> -value*
<b>Age, years</b>			
Mean (range)	42.2 (13–72)	40.4 (13–70)	0.07
<b>Age, n (%)</b>			
13 to <18 years	4 (1)	8 (3)	
18 to <65 years	292 (97)	286 (96)	
≥65 years	5 (2)	5 (2)	
<b>Sex, n (%)</b>			
Male	203 (67)	187 (63)	0.23
<b>Region, n (%)</b>			
United States	117 (39)	121 (40)	0.74
Non–United States <sup>††</sup>	184 (61)	178 (60)	
<b>Primary underlying diagnosis, n (%)<sup>†††</sup></b>			
Chronic myelogenous leukemia	98 (33)	104 (35)	0.60
Acute myeloid leukemia	81 (27)	66 (22)	0.18
Non-Hodgkin’s lymphoma	40 (13)	35 (12)	0.62
Acute lymphoblastic leukemia	25 (8)	36 (12)	0.14
Myelodysplastic disorder	19 (6)	13 (4)	0.36

Chronic lymphoblastic leukemia	10 (3)	11 (4)	0.83
Multiple myeloma	10 (3)	12 (4)	0.67
Aplastic anemia	8 (3)	7 (2)	1.0
Hodgkin's lymphoma	2 (1)	7 (2)	0.11
Other	12 (4)	9 (3)	0.66
None	0	1 (<1)	
<b>GVHD class at baseline, n (%)</b>			
Acute Grade I	3 (1)	1 (<1)	0.62
Acute Grade II	135 (45)	136 (45)	0.94
Acute Grade III	52 (17)	54 (18)	0.83
Acute Grade IV	12 (4)	6 (2)	0.23
Chronic limited	2 (1)	1 (<1)	1.0
Chronic extensive	96 (32)	99 (33)	0.79
Missing	1 (<1)	2 (1)	
<b>Time from transplant to baseline, n (%)</b>			
<30 days	45 (15)	37 (12)	
30 to 60 days	98 (33)	103 (34)	
61 to 100 days	32 (11)	37 (12)	
≥101 days	124 (41)	121 (40)	
Missing	2 (1)	1 (<1)	
Mean (SD)	156.1 (222.2)	171.6 (262.3)	0.46
Median	63	64	
Range	0–1858	0–1692	

<b>Prior history of invasive yeast or mould infection, n (%)</b>	<b>8 (3)</b>	<b>15 (5)</b>	0.14
<b>T-cell depleted stem-cells transplanted at latest transplant prior to study entry, n (%)</b>	<b>37 (12)</b>	<b>32 (11)</b>	0.61
<b>Body irradiation on or before transplant date, n (%)</b>	<b>135 (45)</b>	<b>146 (49)</b>	0.39
<b><i>Aspergillus</i> antigen</b>			
Positive ( $\geq 0.5$ at Baseline)	21 (7)	30 (10)	0.19
Negative	259 (86)	243 (81)	
Missing	21 (7)	26 (9)	
<b>Neutropenia (baseline ANC <math>&lt; 500/\text{mm}^3</math>), n (%)</b>			
Yes	6 (2)	1 ( $< 1$ )	0.12
No	277 (92)	280 (94)	
Missing	18 (6)	18 (6)	
<b>CMV (pp65-antigen or DNA-PCR) during treatment, n (%)</b>	<b>96 (32)</b>	<b>78 (26)</b>	0.13
<b>Baseline corticosteroids (mg/kg/day), n (%)</b>			
$\geq 2.0$	41 (14)	32 (11)	0.32
$< 2.0$ but $\geq 1.0$	107 (36)	129 (43)	0.07
$< 1.0$	142 (47)	127 (42)	0.25
Dose Unknown	10 (3)	10 (3)	

None	1 (<1)	1 (<1)	
<b>Number of immunosuppressive agents at baseline, n (%)</b>			
1	64 (21)	48 (16)	0.12
2	151 (50)	168 (56)	0.14
≥3	85 (28)	82 (27)	0.86
None	1 (<1)	1 (<1)	
<b>Duration of prior antifungal therapy on or before first dose</b>			
Mean (SD)	26.4 (39)	35.3 (82)	0.09
Median	16	19	
Range	0–254	0–1002	
<b>Prior antifungal therapy on or before baseline, n (%)</b>			
Any antifungal	211 (70)	207 (69)	0.86
Amphotericin B	48 (16)	45 (15)	0.82
Ketoconazole	2 (1)	0	0.50
Fluconazole	181 (60)	183 (61)	0.80
Itraconazole	28 (9)	33 (11)	0.50
Caspofungin	1 (<1)	2 (1)	0.62
Miconazole	0	2 (1)	

<sup>††</sup> Canada, Mexico, Europe, Australia, Central and South America, Taiwan, and Singapore.

<sup>†††</sup> Patients with multiple primary diagnoses are counted in each primary diagnosis category.

\* T-test used for continuous variables; Fisher's Exact test used for categorical variables.

**TABLE B: Patient Demographics, Baseline Disease Characteristics, and Invasive Fungal Infection Risk Factors During the Exposure Period (“While on Therapy”)**

	Exposure Period	
	Posaconazole (n=291)	Fluconazole (n=288)
<b>Age, years</b>		
Mean (range)	42.3 (13–72)	40.3 (13–70)
<b>Age, n (%)</b>		
13 to <18 years	4 (1)	8 (3)
18 to <65 years	283 (97)	276 (96)
≥65 years	4 (1)	4 (1)
<b>Sex, n (%)</b>		
Male	196 (67)	180 (63)
<b>Region, n (%)</b>		
United States	111 (38)	116 (40)
Non–United States*	180 (62)	172 (60)
<b>Primary underlying diagnosis, n (%)<sup>†</sup></b>		
Chronic myelogenous leukemia	94 (32)	99 (34)
Acute myeloid leukemia	79 (27)	64 (22)
Non-Hodgkin’s lymphoma	39 (13)	35 (12)
Acute lymphoblastic leukemia	25 (9)	35 (12)
Myelodysplastic disorder	18 (6)	12 (4)

Chronic lymphoblastic leukemia	10 (3)	10 (3)
Multiple myeloma	10 (3)	12 (4)
Aplastic anemia	8 (3)	7 (2)
Hodgkin's lymphoma	2 (1)	7 (2)
Other	10 (3)	9 (3)
None	0	0
<b>GVHD class at baseline, n (%)</b>		
Acute Grade I	3 (1)	1 (<1)
Acute Grade II	132 (45)	134 (47)
Acute Grade III	49 (17)	53 (18)
Acute Grade IV	11 (4)	5 (2)
Chronic limited	2 (1)	0
Chronic extensive	93 (32)	95 (33)
Missing	1 (<1)	0
<b>Time from transplant to baseline, n (%)</b>		
<30 days	44 (15)	37 (13)
30 to 60 days	96 (33)	99 (34)
61 to 100 days	32 (11)	36 (13)
≥101 days	118 (41)	116 (40)
Missing	1 (<1)	0
Mean (SD)	157.9 (232.47)	172.9 (265.68)
Median	63	64
Range	0–1858	15–1692
<b>Prior history of invasive yeast or mould infection, n (%)</b>	<b>7 (2)</b>	<b>15 (5)</b>

<b>T-cell depleted stem-cells transplanted at latest transplant prior to study entry, n (%)</b>	<b>36 (12)</b>	<b>30 (10)</b>
<b>Body irradiation on or before transplant date, n (%)</b>	<b>130 (45)</b>	<b>140 (49)</b>
<b><i>Aspergillus</i> antigen</b>		
Positive ( $\geq 0.5$ at Baseline)	21 (7) <sup>††</sup>	30 (10) <sup>††</sup>
Negative	257 (88)	242 (84)
Missing	13 (4)	16 (6)
<b>Neutropenia (baseline ANC <math>&lt; 500/\text{mm}^3</math>), n (%)</b>		
Yes	6 (2)	1 ( $< 1$ )
No	271 (93)	275 (95)
Missing	14 (5)	12 (4)
<b>CMV positivity (pp65-antigen or DNA-PCR) during treatment, n (%)</b>	<b>96 (33)</b>	<b>76 (26)</b>
<b>Baseline corticosteroids (mg/kg/day), n (%)</b>		
$\geq 2.0$	40 (14)	32 (11)
$< 2.0$ but $\geq 1.0$	105 (36)	126 (44)
$< 1.0$	140 (48)	125 (43)
Dose Unknown	5 (2)	5 (2)
None	1 ( $< 1$ )	0
<b>Number of immunosuppressive agents at baseline, n (%)</b>		
1	62 (21)	45 (16)
2	146 (50)	164 (57)
$\geq 3$	82 (28)	79 (27)
None	1 ( $< 1$ )	0

<b>Duration of prior antifungal therapy on or before first dose</b>		
Mean (SD)	26.3 (39)	34.9 (83)
Median	16	19
Range	0–254	0–1002
<b>Prior antifungal therapy on or before baseline, n (%)</b>		
Any antifungal	203 (70)	200 (69)
Amphotericin B	45 (15)	44 (15)
Ketoconazole	1 (<1)	0
Fluconazole	174 (60)	177 (61)
Itraconazole	25 (9)	31 (11)
Caspofungin	1 (<1)	2 (1)
Miconazole	0	2 (1)

\* Canada, Mexico, Europe, Australia, Central and South America, Taiwan, and Singapore.

† Patients with multiple primary diagnoses are counted in each primary diagnosis category.

††  $P=0.189$  by Fisher's Exact test

GVHD indicates graft-versus-host disease; ANC, absolute neutrophil count; CMV, cytomegalovirus; PCR, polymerase chain reaction.

**TABLE C:****Usage Rates of Systemic Antifungals During the Exposure Period (“While on Treatment” Phase)**

The table presented below indicates that approximately 10 percent of subjects required temporary treatment with other systemic antifungals while receiving the study medication for prophylaxis:

<b>Medication</b>	<b>Posaconazole</b>	<b>Fluconazole</b>
	n = 291 n (%)	n = 288 n (%)
Any antifungal	31 (11)	29 (10)
Amphotericin B	12 (4)	17 (6)
Ketoconazole	1 (<1)	0
Fluconazole	17 (6)	15 (5)
Itraconazole	3 (1)	3 (1)
Caspofungin	1 (<1)	4 (1)
Flucytosine	0	1 (<1)

**TABLE D: Number (Percent) of Patients with Treatment-related Treatment-emergent Adverse Events: Occurrence of at Least 2 Percent in Either Treatment Group (ITT Patients)**

<b>Body System/Preferred Term, n (%)</b>	<b>Posaconazole (n=301)</b>	<b>Fluconazole (n=299)</b>
<b>Patients Reporting Any Adverse Event</b>	<b>107 (36)</b>	<b>115 (38)</b>
<b>Body as a whole – general disorders</b>		
Anorexia	3 (1)	7 (2)
Dizziness	4 (1)	5 (2)
Drug level altered	5 (2)	2 (1)
Fatigue	4 (1)	6 (2)
Headache	3 (1)	8 (3)
Weakness	3 (1)	5 (2)
<b>Cardiovascular disorders, general</b>		
Hypertension	2 (1)	5 (2)
<b>Central and peripheral nervous system disorders</b>		
Tremor	4 (1)	6 (2)
<b>Disorders of the eye</b>		
Vision Blurred	3 (1)	5 (2)
<b>Gastrointestinal system disorders</b>		
Abdominal pain	4 (1)	7 (2)
Constipation	1 (<1)	5 (2)
Diarrhea	8 (3)	12 (4)
Dyspepsia	3 (1)	6 (2)

Nausea	22 (7)	28 (9)
Vomiting	13 (4)	15 (5)
<b>Liver and biliary system disorders</b>		
Bilirubinemia	8 (3)	5 (2)
Increased $\gamma$ -glutamyl-transferase	9 (3)	7 (2)
Increased hepatic enzymes	8 (3)	7 (2)
Increased aspartate aminotransferase	8 (3)	3 (1)
Increased alanine aminotransferase	9 (3)	4 (1)
Increased alkaline phosphatase	5 (2)	5 (2)
<b>Renal and urinary system disorders</b>		
Blood creatinine increased	6 (2)	5 (2)
<b>Special senses other, disorders</b>		
Taste perversion	3 (1)	5 (2)

**TABLE E: Patients with Treatment-related Serious Adverse Events.**

Overall frequency of treatment-related serious adverse events was comparable in each group: 13 percent in the posaconazole group versus 10 percent in the fluconazole group.

<b>Serious Adverse Events, n (%)</b>	<b>Posaconazole (n = 301)</b>	<b>Fluconazole (n = 299)</b>
<b>Autonomic nervous system disorders</b>		
Flushing	0	1 (<1)
<b>Body as a whole – general disorders</b>		
Anorexia	1 (<1)	0
Asthenia	0	1 (<1)
Dizziness	1 (<1)	0
Drug interaction	1 (<1)	1 (<1)
Drug level altered	2 (1)	1 (<1)
Fever	0	1 (<1)
Fungal infection	0	1 (<1)
Hypoxia	1 (<1)	0
Weakness	0	1 (<1)
<b>Cardiovascular disorders - general</b>		
Hypotension	0	1 (<1)
<b>Central and peripheral nervous system disorders</b>		
Areflexia	1 (<1)	0
Ataxia	1 (<1)	0
Blurred vision	1 (<1)	0
Confusion	0	1 (<1)
Convulsions	1 (<1)	0
Dystonia	1 (<1)	0
Encephalopathy	1 (<1)	0

Hypoesthesia	1 (<1)	0
Meningism	1 (<1)	0
Meningitis	1 (<1)	0
Mental status, altered	1 (<1)	0
Migraine	1 (<1)	0
Neuropathy	1 (<1)	0
Somnolence	0	2 (1)
Speech Disorders	0	1 (<1)
Stupor	1 (<1)	0
Tremor	1 (<1)	0
Twitching	1 (<1)	0
<b>Disorders of blood and lymphatic system</b>		
Anemia	1 (<1)	1 (<1)
Hemolytic uremic syndrome	1 (<1)	0
Neutropenia	0	1 (<1)
Pancytopenia	0	1 (<1)
<b>Disorders of the immune system</b>		
Graft vs. host disease, aggravated	1 (<1)	0
<b>Gastro-intestinal system disorders</b>		
Diarrhea	2 (1)	1 (<1)
Duodenitis	0	1 (<1)
Dysphagia	0	1 (<1)
Gastritis	0	1 (<1)
Gastrointestinal hemorrhage	0	1 (<1)

Ileus	0	1 (<1)
Intestinal ulceration	0	1 (<1)
Nausea	4 (1)	0
Vomiting	4 (1)	1 (<1)
<b>Heart rate and rhythm disorders</b>		
Bundle branch block	1 (<1)	0
ECG abnormal	1 (<1)	0
Fibrillation atrial	1 (<1)	1 (<1)
<b>Injury and poisoning</b>		
Drug toxicity (NOS*)	2 (1)	0
Overdose (NOS)	0	1 (<1)
<b>Liver and biliary system disorders</b>		
Bilirubinemia	3 (1)	3 (1)
Bilirubinemia aggravated	2 (1)	0
Hepatic failure	0	1 (<1)
Abnormal hepatic function	0	3 (1)
Hepatitis	1 (<1)	0
Hepatocellular damage	4 (1)	0
Increased alanine aminotransferase	2 (1)	1 (<1)
Increased alkaline phosphatase	1 (<1)	0
Increased aspartate aminotransferase	2 (1)	1 (<1)
Increased $\gamma$ -glutamyl-transferase	5 (2)	3 (1)
Increased hepatic enzymes	6 (2)	1 (<1)
Jaundice	1 (<1)	0

<b>Metabolic and nutritional disorders</b>		
Hyperkalemia	1 (<1)	1 (<1)
Hypomagnesemia	1 (<1)	0
<b>Musculo-skeletal system disorders</b>		
Muscle weakness	1 (<1)	1 (<1)
<b>Platelet, bleeding and clotting disorders</b>		
Bruising	0	1 (<1)
Coagulation disorder	0	1 (<1)
Thrombocytopenia	2 (1)	0
Thrombotic thrombocytopenic purpura	1 (<1)	0
<b>Psychiatric disorders</b>		
Psychosis	1 (<1)	0
<b>Renal and urinary system disorders</b>		
Creatinine clearance decreased	1 (<1)	0
Hematuria	1 (<1)	0
Increased blood creatinine	1 (<1)	1 (<1)
Renal calculus	1 (<1)	0
Renal failure	1 (<1)	1 (<1)
Renal failure, acute	1 (<1)	0
Renal function, abnormal	1 (<1)	0
Renal insufficiency	0	2 (1)
Renal insufficiency, aggravated	1 (<1)	0
<b>Respiratory system disorders</b>		
Coughing	1 (<1)	1 (<1)

Coughing, aggravated	0	1 (<1)
Pharyngeal disorder	0	1 (<1)
Rales	1 (<1)	0
<b>Skin and subcutaneous tissue disorders</b>		
Blood blister	0	1 (<1)
Pruritus	1 (<1)	0
Rash maculopapular	1 (<1)	0
<b>Vascular (extracardiac) disorders</b>		
Deep venous thrombosis	1 (<1)	0
Embolism, arterial	0	1 (<1)
Embolism, pulmonary	1 (<1)	0
Thrombosis	0	1 (<1)

\* not related to study drug

NOS = not otherwise specified.

**TABLE F: Disposition of Subjects During the Fixed Treatment Period (Primary Time Period) by Treatment Group: (All Randomized Subjects)**

After randomization, patients were treated for up to 112 days or until a protocol-specified end point (breakthrough IFI, adverse event requiring discontinuation, or death) was reached.

Patients who discontinued treatment for reasons other than death were followed for the full 112 days.

<b>Disposition</b>	<b>Posaconazole (N=301)</b>	<b>Fluconazole (N=299)</b>
	<b>n(%)</b>	<b>n(%)</b>
<b>Subjects who completed primary time period</b>	207 (69)	192 (64)
<b>Subjects who discontinued from the study during the primary time period</b>	94 (31)	105 (35)
Administrative	1 (<1)	0
Adverse event	57 (19)	55 (18)
Did not meet protocol eligibility	3 (1)	5 (2)
Lost on follow up	1 (<1)	0
Noncompliance with protocol	6 (2)	4 (1)
Subject did not wish to continue	15 (5)	12 (4)
Treatment failure	11 (4)	29 (10)
<b>Disposition unknown</b>	0	2 (1)

Subjects who died during the fixed treatment period (n=58 [19 percent] posaconazole versus n=59 [20 percent] fluconazole) are included usually in the category of discontinuation due to an adverse event or treatment failure.

**TABLE G: Proven/Probable IFIs Identified at Various Defined Study Periods**

The table below lists the number of IFI's identified at various defined study periods for each treatment group.

<b>Study Period</b>	<b>Posaconazole</b>	<b>Fluconazole</b>
Observation Period (Any Time)	<b>20</b>	<b>42</b>
Fixed Treatment Period (Primary Time Period)	<b>16</b>	<b>27</b>
Post Fixed Treatment Period (post Primary Time Period)	<b>4</b>	<b>15</b>
Exposure Period ("While on Treatment")	<b>7</b>	<b>22</b>
Post Exposure Period (post "While on Treatment")	<b>12</b>	<b>20</b>

**TABLE H: Incidence of Proven or Probable Invasive Fungal Infections by Selected Risk Factors During the Exposure (“While on Treatment”) Period**

IFI Risk Factor	While on Treatment			
	Posaconazole (n=291)		Fluconazole (n=288)	
	n	Patients With IFI, n (%)	n	Patients With IFI, n (%)
<b><i>GVHD Class</i></b>				
Acute Grade I	3	0	1	0
Acute Grade II	132	2 (2)	134	8 (6)
Acute Grade III	49	4 (8)	53	11 (21)
Acute Grade IV	11	0	5	0
Chronic limited	2	0	0	0
Chronic extensive	93	1 (1)	95	3 (3)
<b><i>Aspergillus antigen at baseline</i></b>				
Positive ( $\geq 0.5$ at Baseline)	21	1 (5)	30	5 (17)
No	257	6 (2)	242	17 (7)
Missing	13	0	16	0
<b>Baseline corticosteroids (mg/kg/day)</b>				
$\geq 2.0$	40	2 (5)	32	5 (16)
$< 2.0$ but $\geq 1.0$	105	3 (3)	126	9 (7)
$< 1.0$ but $\geq 0.4$	107	1 (1)	98	6 (6)
$< 0.4$ but $\geq 0$	33	0	27	1 (4)

Dose unknown	5	1 (20)	5	1 (20)
None	1	0	0	0
<b>CMV positive (pp65- antigen or DNA-PCR) during treatment</b>				
Yes	96	2 (2)	76	10 (13)
No	195	5 (3)	212	12 (6)
<b>No. of immunosuppressive agents at baseline</b>				
1	62	2 (3)	45	4 (9)
2	146	2 (1)	164	12 (7)
≥3	82	3 (4)	79	6 (8)
None	1	0	0	0
<b>Region</b>				
United States	111	5 (5)	116	12 (10)
Non–United States	180	2 (1)	172	10 (6)