Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Voriconazole

Proprietary Product Name: Vfend

Sponsor: Pfizer Australia Pty Ltd

Date of CER:
30 August 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	adverse event
CDS	core data sheet
CI	confidence interval
CRF	case report form
GFR	glomerular filtration rate
GvHD	graft versus host disease
HSCT	haematopoietic stem cell transplantation
IBD	international birth date
IFI	invasive fungal infection
ITT	intention-to-treat
ITZ	itraconazole
LFT	liver function test
MA	myeloablative
MAH	market authorisation holder
MITT	modified intention-to-treat
NMA	non-myeloablative
NSL	non-serious listed
PP	per protocol
PSUR	periodic safety update report
SAE	serious adverse event
SCC	squamous cell carcinoma
SCT	stem cell transplantation
VRZ	voriconazole
WBC	white blood count

1. Clinical rationale

This submission seeks to add the additional indication of "Use for prophylaxis against the development of serious invasive fungal infections (IFI) in high-risk patients, such as hematopoietic stem cell transplant (HSCT) recipients".

1. Vfend (voriconazole) is registered in Australia for the treatment of severe invasive fungal infections.
2. IFI are major causes of morbidity and mortality in allogeneic HSCT recipients.
3. IFI caused by Candida species were more frequent during the pre-engraftment period but are now reduced by the use of fluconazole as prophylaxis. However, there is a need for a well-tolerated antifungal agent that can be used to prevent both Aspergillus and Candida infections during both phases after allogeneic HSCT.
4. The following antifungal drugs have been approved with prophylaxis indications although approvals have not been granted in all countries worldwide: micafungin, fluconazole, itraconazole (ITZ) and posaconazole. Micafungin and fluconazole are primarily used for prevention of IFI from Candida spp., and in Australia, posaconazole is indicated for the prophylaxis of IFI among patients 13 years of age and older, who are at high risk of developing these infections, such as patients with prolonged neutropenia or HSCT recipients. Itraconazole is approved for prophylaxis throughout Europe and in Australia.
5. A pivotal multi-centre study has been conducted to demonstrate non-inferiority of voriconazole versus itraconazole in regards of primary prophylaxis of IFI among recipients of allogeneic HSCT.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The dossier's pivotal study is termed "A1501073". It has been designed and conducted as a prospective open-label, multi-centre study comparing voriconazole to itraconazole for the primary prophylaxis of IFI in subjects with allogeneic HSCT. Supportive data is provided by study A1501038; a prospective, open-label, non-comparative, multi-centre study for the secondary prophylaxis of IFI with voriconazole in patients with allogeneic stem cell transplants.

2.2. Good clinical practice

Studies A1501073 and A1501038 were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.

3. Pharmacokinetics

Neither study A1501073 nor study A1501038 included pharmacokinetic evaluations.

4. Pharmacodynamics

Neither study A1501073 nor study A1501038 included pharmacodynamic evaluations.

5. Dosage selection for the pivotal studies

See *Clinical Efficacy.*

6. Clinical efficacy

6.1. Study A1501073

6.1.1. Study design:

A prospective, multicenter, randomised, comparative, open-label study which enrolled subjects ≥12 years of age in 50 centres in 12 countries in N- America, Europe, N-Africa and the Russian Federation.

6.1.2. Study objectives:

6.1.2.1. Primary objective

To compare the success of antifungal prophylaxis with voriconazole versus itraconazole at 180 days post HSCT transplant. Success was measured using a composite endpoint of survival to Day 180 with no breakthrough IFI and no discontinuation of study drug for >14 days in total during the 100-day prophylaxis.

6.1.2.2. Secondary objectives

- Success of antifungal prophylaxis (as defined above), but at 100 days post transplant

Comparisons of:

- Time to breakthrough IFI.
- Rates of occurrence of breakthrough IFI.
- Survival to 180 days post transplant.
- Safety and tolerability of the 2 study treatments.
- Time to discontinuation of study treatment.
- Durations of study drug treatment (solid or liquid oral formulations and IV formulation) and rates of empirical therapy.
- Use of other systemic antifungal agents as empirical or therapeutic treatment.
- Reasons for discontinuation of study treatment.
- Survival 1 year after transplant (which will be reported separately).
- Subject-assessed tolerability of therapy.
- Use of healthcare resources.

6.1.3. Study methods:

Location: The study was conducted at 50 centres in Canada (5), Czech Republic (2), Egypt (1), France (10), Greece (2), Jordan (1), Portugal (2), Russian Federation (2), Spain (10), Switzerland (2), Turkey (2) and the UK (11).

Sample size: The overall number of planned enrolment was 500 subjects, 250 randomised to each group. The actual enrolment was 503 of which 489 received at least one dose of study treatment (modified intention-to-treat population [MITT]). 24 treated subjects from one site

were excluded from all efficacy analyses due to GCP violations. 234 were treated with VRZ and 255 with ITZ. Of these, 24 treated subjects from Site 1028 (10 in the voriconazole treatment group and 14 in the itraconazole treatment group) were included in all safety analyses, but excluded from the efficacy analyses (Table 1).

Table 1. Study A1501073: Study Population

	Number (%) of Subjects	
	Voriconazole	Itraconazole
Screened	534	
Randomized to study treatment	503	
Randomized	243	260
Treated	234	255
Completed[a]	176 (75.2)	175 (68.6)
Discontinued before Day 180 Visit[b]	58 (24.8)	80 (31.4)
Died[c]	35 (15.0)	38 (14.9)
Adverse event – related to treatment	8 (3.4)	7 (2.7)
Adverse event – unrelated to treatment	7 (3.0)	6 (2.4)
Failure of prophylaxis	1 (0.4)	1 (0.4)
Fungal breakthrough infection	0	1 (0.4)
Lost to follow-up	0	1 (0.4)
Other reasons[d]	5 (2.1)	14 (5.5)
Subject no longer willing to participate in study	2 (0.9)	12 (4.7)
Analyzed for efficacy[e]		
Intent-to-Treat	224 (95.7)	241 (94.5)
Modified Intent-to-Treat	224 (95.7)	241 (94.5)
Per Protocol	185 (79.1)	199 (78.0)
Analyzed for adverse events (Safety Population)	234 (100.0)	255 (100.0)
Analyzed for clinical laboratory results[f]	221 (94.4)	236 (92.5)

Source: Tables 13.1.1, 13.1.1x, 13.1.2, 13.1.2x, and 13.1.3; Appendix B1.2

[a]Includes subjects from Site 1028 (7 who completed in the voriconazole group and 9 who completed in the itraconazole group) who were evaluated for safety only.

[b]Includes subjects from Site 1028 (including 1 subject in the itraconazole group who discontinued from the study due to death) who were evaluated for safety only.

[c]Additional deaths were recorded among subjects who discontinued for reasons other than death and then died before Day 180.

[d]Other reasons for discontinuation included: participation in another clinical trial, allogeneic transplant relapse, received more than 14 days of an empirical antifungal treatment, received a new transplant, suspected fungal infection, failure to complete visits, and investigator decision.

[e]A total of 24 treated subjects from Site 1028 (10 from voriconazole and 14 from itraconazole) were evaluated for safety only. Percentages for the Intent-to-Treat, modified Intent-to-Treat, and Per Protocol populations in this table were derived from the Safety population.

[f]In order to be analyzed for laboratory results, subjects had to have a baseline value and at least 1 posttreatment value for a laboratory parameter.

Study duration: The first subject visit was on the 8th of March 2006 and the last one on the 10th of February 2009. Administration of the prophylactic regimen began on the day of HSCT or at latest 48 hours after. Study drug administration continued until at least Day 100 or until a probable or definite breakthrough IFI developed, the subject died or permanently discontinued the study drug, whichever occurred first. Study drug was administered for a maximum of 180 days after HSCT if the subject:

- Received prednisone (> 0.2 mg/kg), OKT3 (muromonab - CD3), or mycophenolate mofetil, infliximab, daclimuzab, Campath 1H (alemtuzamab).
- Received ATG (antithymocyte globulin) or had received ATG within the 4 weeks prior to Day 100.
- Was neutropenic (polymorphonuclear neutrophils [PMN] < 500/mm3) or lymphopenic (absolute lymphocyte count [ALC] < 500/mm3) or had been neutropenic/lymphopenic within the 10 days prior to Day 100 (or at any time between Day 100 and Day 180).
- Experienced Graft versus Host Disease (GvHD) or another cause of immunosuppression that was expected to prolong the risk for the development of a fungal infection beyond day 100.

An assessment of success for the primary endpoint was only made if the subject survived until Day 180 without developing definite or probable IFI and completed at least 100 days of prophylaxis. Discontinuation of study medication for >14 days in total during the prophylaxis period, regardless of reason, automatically classified the subject as a failure.

6.1.3.1. Eligibility criteria/Study population:

Inclusion criteria to be eligible for enrolment into the trial were:

- Male or female, ≥ 12 years of age.
- Allogeneic HSCT for acute leukaemia (acute myeloid leukaemia [AML], acute lymphatic leukaemia [ALL], or myelodysplastic syndrome), failure of therapy for lymphoma or transformation of chronic myeloid leukaemia.
- Signed and dated informed consent.
- Females of childbearing potential with a negative serum beta-human chorionic gonadotropin pregnancy test at Screening using an approved method of contraception.

6.1.3.2. Exclusion criteria were:

- Possible, probable or proven IFI at study entry or at any time within 6 months prior to study entry, defined according to the "consensus criteria." (EORTC, 2004).
- Previous history of zygomycosis (e.g. *Mucor, Absidia, Rhizopus*).
- Use of any systemically active antifungal agent within the 7 days prior to study entry.
- Allergy to study drugs or any excipient.
- Abnormal laboratory test results, defined as impaired hepatic function, as shown by transaminases or alkaline phosphatase > 5 x upper limit of normal (ULN), or bilirubin > 2.5 mg/dL.
- Severe disease, other than underlying condition, considered likely to jeopardize the planned termination of the study (e.g., acute myocardial infarction, unstable angina pectoris, potentially pro-arrhythmic conditions such as cardiac impairment due to previous cardiotoxic chemotherapy, previous torsades de pointes, prolongation of the QT interval >450 msec for men or >470 msec for women).
- Concomitant use of sirolimus, ergot alkaloids, terfenadine, astemizole, cisapride, pimozide, quinidine, carbamazepine, rifampicin, phenobarbital, ritonavir, efavirenz, or St. John's Wort which might have interfered with the evaluation of study drugs during the study.
- Alcohol and/or any other drug abuse.
- Previous participation in this trial.
- Unable and/or unlikely to comprehend and/or follow the protocol.
- Participation in any other studies involving investigational products, concomitantly or within 30 days prior to entry in the study.
- Anticipated survival less than 1 month.

Stratification: Subjects were stratified by their conditioning regimen (myeloablative [MA] or non-myeloablative [NMA]) and the relatedness of the donor (matched related or mismatched/unrelated). Randomisation was blocked by centre.

Treatment protocol: the treatment allocation was open label. Subjects started IV therapy with voriconazole or itraconazole for 2 days, in order to rapidly reach adequate blood levels, before switching to oral therapy on Day 2 of prophylaxis. Oral voriconazole followed the schedule in Table 2. Subjects could be switched to intravenous therapy in case of mucositis or gut GvHD.

Table 2. Study A1501073 Voriconazole dosing for adults and children >12 years of age

		Oral	
	Intravenous	Tablet or Powder for Oral Suspension for Subjects 40 kg and above	Tablet or Powder for Oral Suspension for Subjects less than 40 kg
Loading Dose Regimen (first 24 hours)	6 mg/Kg every 12 hours	N/A	N/A
Maintenance Dose (after first 24 hours)	4 mg/Kg twice daily	200 mg twice daily	100 mg twice daily

Itraconazole was administered as oral solution (Sporanox Liquid), dosed at 200mg of itraconazole PO BID as the primary formulation. For optimal absorption, Sporanox liquid should be taken without food. Subjects are advised to refrain from eating for at least 1 hour after intake.

IV formulation (Sporanox IV) at 200mg BID as a loading dose on Days 0 and 1. Thereafter 200mg OD if subjects had mucositis or gut GvHD which might compromise oral absorption.

Sporanox Capsules at 200 mg BID where subjects are temporarily unable or unwilling to continue on the oral solution, capsules may be taken for a total of 14 days (short, < 5 day, periods recommended).

Monitoring: Evaluation visits were carried out at Screening (Days - 6 to - 3), Baseline (Day 0), and at Days 2, 14, 28, 56, 100, 140 and Day 180 and whenever study drug was permanently discontinued. There was a Follow-up at Day 210 for adverse event (AE) monitoring and signs of fungal infection and a second Follow-up 1 year after transplant to assess long term survival only.

A Data Review Committee (DRC), consisting of 5 investigators and 1 radiologist and attended by the clinician and study manager, convened to review blinded data associated with all suspected IFIs and to verify each cause of death.

The collection of plasma samples to assess the levels of study drug in blood was mandatory at Day 14. Further plasma samples to assess study drug levels in blood were required at the time of any breakthrough IFI. For itraconazole subjects, a sample was also taken after capsule use, if applicable.

Statistical methods: to be a success as defined for the primary efficacy analysis a subject had to be alive and without proven or probable IFI by visit 9 (day 180) and have been taken the assigned medication during the 100 days of study drug prophylaxis (with no discontinuation >14 days; itraconazole capsules in the ITZ group for ≤14 days).

The primary analysis was based on the modified ITT (MITT) population (subjects who took at least one dose of randomized study drug and had undergone allogeneic HSCT). The difference between the proportions of successes in each treatment arm, and associated approximate 2-sided 95% confidence interval (CI), was calculated. The primary analysis was stratified for both conditioning regimen and relatedness of donor. Missing values of the primary endpoint were set to failure.

The estimated difference between the 2 responder rates, adjusted for this 4-level factor, together with the associated approximate 2-sided 95% CI for this difference was evaluated

using the Fleiss method. The stratified analysis involved the use of weighted averages for each difference, with the weight defined as the reciprocal of the square of the standard error.

The primary analysis was intended to demonstrate non-inferiority of antifungal prophylaxis with voriconazole compared to itraconazole at Day 180 post transplant. Non-inferiority was inferred if the lower limit of the 2-sided 95% CI for the difference between the voriconazole and itraconazole treatment groups in the proportion of subjects classified as a success at Day 180 post transplant was above – 10%.

If testing for non-inferiority was successful, then an assessment of superiority of voriconazole over itraconazole was carried out. Superiority was achieved if the 2-sided 95% CI for the difference between the voriconazole and itraconazole treatment groups in the proportion of subjects classified as a success at Day 180 post transplant did not include zero and was positive.

In addition, an identical analysis of the primary endpoint was calculated based on the per protocol (PP) population. No analysis was performed on the ITT population as identity was expected between the MITT and the ITT population.

Moreover, the primary endpoint was analysed with logistic regression. The terms fitted in the model were country, treatment, conditioning regimen and relatedness of donor. The adjusted odds ratio of success and its corresponding 95% CI was calculated.

The secondary key endpoint success at day 100 was analysed with the same methods as the primary endpoint, using MITT and PP population. All other analyses were based on the MITT unless the results differed substantially between populations and calculated unadjusted proportions for each treatment arm together with approximated 95% CI and p-values. Some of the secondary endpoints were calculated with logistic regression.

All time-to-event endpoints were analysed using survival analysis methodology. Survivor functions of each time-to-event endpoint for each treatment were separately estimated using the Kaplan-Meier method. All subjects who did not experience the relevant event were treated as right-censored observations.

6.1.4. Demographics and baseline characteristics:

The majority of subjects in both groups were male; mean age was approximately 43 years (range 11 to 70 years) and 90% were White. The majority of subjects had peripheral blood type transplants, 177 (76%) in the VRZ and 195 (77%) in the ITZ group. The majority of subjects had HLA identical sibling donors: 127 (54%) in the VRZ group and 136 (53%) in the ITZ group.

The conditioning regimen was myeloablative (MA) for the majority of subjects: 130 (56%) in the VRZ group and 149 (58%) in the ITZ group. The most commonly reported primary diagnosis was acute myeloid leukaemia: 102 subjects in the VRZ group and 119 subjects in the ITZ group with a mean duration since first diagnosis of 0.9 years for both treatment groups.

6.1.5. Prior and concomitant treatments

Almost all subjects (99%) reported taking medications prior to the start of the study. The most frequently reported prior medications were cyclosporine (404 subjects) and acyclovir (369 subjects). All subjects (100%) took concomitant medications at some time during the study; the most frequently reported were cyclosporine (442 subjects) and acyclovir (422 subjects).

Less than half of all subjects (42%) reported prior nondrug treatments; the most frequently reported was radiotherapy (87 subjects). The majority of subjects (74%) used concomitant nondrug treatments at some time during the study; the most frequently reported were platelet transfusion (165 subjects) and chest X-ray (157 subjects).

6.1.6. Treatment duration

For the VRZ group, the median duration of treatment was 97 days (range 1- 258 days) and for the ITZ group 68 days (range 3- 223 days).

6.1.7. Results

6.1.7.1. Primary evaluation – Success of prophylaxis at Visit 9 (Day 180)

The number and percentage of subjects who were a success for the antifungal prophylaxis at Day 180 were 109 (48.7%) and 80 (33.2%) for VRZ and ITZ, respectively. This represented a difference of 15.5% between the unadjusted responder rates in favour of VRZ. The approximate 95% CI for this difference was (6.6%, 24.3%). The difference adjusted for the randomisation strata are depicted in Table 3.

Table 3. Study A1501073: Summary of success of prophylaxis at visit 9 (Day 180) test for non-inferiority and superiority - MITT Population

Randomization Strata	Number of Subjects (n)		Number (%) of Responders		Difference in Proportions
	Voriconazole N=224	Itraconazole N=241	Voriconazole	Itraconazole	
Myeloablative & matched related	66	85	39 (59.1%)	38 (44.7%)	14.4%
Myeloablative & mismatched/unrelated	59	58	31 (52.5%)	15 (25.9%)	26.7%
Non-myeloablative & matched related	58	57	20 (34.5%)	16 (28.1%)	6.4%
Non-myeloablative & mismatched/unrelated	41	41	19 (46.3%)	11 (26.8%)	19.5%
Overall treatment difference in adjusted proportions[a]					16.4%
95% CI for the difference in proportions[a]					(7.7%, 25.1%)
Test for association between the proportion of responders and treatment group[b]					0.0002
Test for homogeneity of association between the proportion of responders and treatment group across randomization strata[c]					0.4080

Source: Table 13.4.2.1.1x
CI = confidence interval
N is the number of subjects in the Modified Intent-to-Treat (MITT) population for the given treatment group. All percentages are calculated using n in the denominator.
Proportions are expressed as percentages.
Non-inferiority is inferred if the lower limit of the 95% CI for the difference in adjusted proportions of subjects classified as a success at Day 180 posttransplant was above -10%. Superiority was achieved if the 95% CI for the difference in adjusted proportions of subjects classified as success at Day 180 posttransplant did not include zero and was positive.
[a]Statistics calculated using Fleiss method.
[b]p-value calculated by referring the test statistic to a chi-square distribution on 1 degree of freedom.
[c]p-value calculated by referring the test statistic to a chi-square distribution on 3 degrees of freedom.

Non-inferiority between the treatments was inferred since the lower confidence limit was above -10%. Moreover, superiority of VRZ over ITZ was achieved since the lower confidence limit was also greater than zero.

The odds ratio (VRZ to ITZ) from a logistic regression model including the covariates treatment, conditioning regimen, relatedness of donor, and country was 2.00 (95% CI: 1.35, 2.95; $p < 0.001$).

Results for the PP population were similar; the unadjusted treatment difference at Visit 9 (Day 180) was 16.2% in favour of VRZ (95% CI: 6.4%, 26.0%); the adjusted treatment difference was 17.3% (95% CI: 7.7%, 27.0%); and the odds ratio from the logistic regression model was 2.06 (95% CI: 1.34, 3.16; p=0.001).

6.1.7.2. Secondary evaluations

6.1.7.2.1. Success of prophylaxis at day 100 (visit 7)

The results for success at Day 100 are shown in Table 4.

Table 4. Study A1501073: Summary of Success of Prophylaxis at Visit 7 (Day 100) – Unadjusted Responder Rates - MITT Population

	Voriconazole N=224	Itraconazole N=241	Difference in Proportions[a] Voriconazole - Itraconazole
Visit 7 (Day 100)			
Number (%) of Responders	121 (54.0%)	96 (39.8%)	14.2%
95% CI[b]			(5.2%, 23.2%)

Source: Table 13.4.2.2.1x
CI = confidence interval
N is the number of subjects in the Modified Intent-to-Treat (MITT) Population for the given treatment group. All percentages are calculated using N in the denominator.
[a]Proportions are expressed as percentages.
[b]Approximate 2-sided 95% confidence interval for the difference in proportions.

The difference adjusted for the randomization strata was 15.4% in favour of VRZ (95%CI: 6.6%, 24.2%, p=0.0006). As for the Day 180 analysis, non-inferiority between the treatments was inferred and superiority of voriconazole over itraconazole was achieved. Also, the results of the logistic regression analysis including covariates treatment, conditioning regimen, relatedness of donor, and country were similar to those observed for Day 180; the odds ratio for the success of prophylaxis at Visit 7 on VRZ relative to ITZ was 1.83 (95% CI: 1.25, 2.67; p=0.002). Results for the PP population were similar to those observed for the MITT population.

6.1.7.2.2. Proportion of subjects with insufficient prophylaxis

Thirty (30) subjects (13.4%) missed Visit 7 in the VRZ group and 39 subjects (16.2%) in the ITZ group. The number and proportion of subjects with insufficient days of prophylaxis (i.e. who missed > 14 days of prophylaxis before Visit 7, took less than 86 days of prophylaxis before Visit 7, or, if randomized to itraconazole, took more than 14 days of ITZ capsules before Visit 7) in the VRZ group was 104 (46.4%) and 147 (61.0%) in the ITZ group, resulting in a treatment difference of -14.6% (95% CI: -23.5%, -5.6%; p=0.0015).

The odds ratio from a logistic regression model including the covariates treatment, conditioning regimen, relatedness of donor, and country was 0.54 (95% CI: 0.37, 0.79; p = 0.001), indicating that the odds of taking an insufficient number of days of prophylaxis by Visit 7 on VRZ were lower than for ITZ.

6.1.7.2.3. Breakthrough fungal infections

A total of 7 subjects developed a breakthrough proven or probable IFI from the start of prophylaxis until Day 180: 3 subjects (1.3%) in the VRZ group and 4 subjects (1.7%) in the ITZ group. IFI was reported earlier for the ITZ treatment group (mean: 77.0 days) compared with VRZ (mean: 119.0 days) where time of IFI was defined as the date of the earliest visit in the study database at which a proven or probable IFI was recorded.

None of the 7 IFIs captured in the study database were fatal; none of the differences between the 2 groups were significant. There was no significant difference in IFI rate between the treatments; log-rank test (p = 0.7221) or Wilcoxon test (p = 0.6304).

Treatment-emergent IFIs were defined as those that occurred at any time from the first day of prophylaxis up until and including 7 days after the last day of prophylaxis. None of the proven or probable IFIs for subjects treated with VRZ were considered treatment-emergent; IFIs in 2 subjects treated with ITZ were considered treatment-emergent.

Data Review Committee members assessed each case of new, suspected fungal infection and confirmed a primary diagnosis of proven or probable IFI with identification of primary disease, by a majority vote. One more itraconazole subject was confirmed by the Data Review Committee as having a probable IFI which was subsequently fatal. This IFI was not captured in the study database due to a limitation in the case report form (CRF) design. A thorough review of the IFI cases was completed and this is the only Data Review Committee confirmed IFI not captured in the study database; the subject died before Day 100 from *aspergillus* infection and was therefore already recorded as a failure for antifungal prophylaxis at both Day 100 and 180.

Hence the recognition of this additional probable IFI does not affect the analysis of the success of prophylaxis at either Day 100 or 180.

6.1.7.2.4. Proportion of subjects who died

Forty (40) subjects (17.9%) in the VRZ group and 44 (18.3%) in the ITZ group died. The mean number of days until death was 106.9 (95% CI: 91.6, 122.1) for the VRZ group and 108.9 (95% CI: 94.8, 122.9) for the ITZ group. There was no significant difference between groups in the survivor functions for the time (in days) from the start of prophylaxis until death; log-rank test (p = 0.7887) or Wilcoxon test (p = 0.8013).

Comparing proportions of subjects who died by Day 180, using complete cases, by fitting a logistic regression model with covariates treatment, conditioning regimen and relatedness of donor, no significant difference between voriconazole and itraconazole was observed (p = 0.672). The same model for the proportions who died by Day 100 was fitted and no significant difference between treatments also observed at this time point (p = 0.956).

6.1.7.3. Other secondary endpoints

Overall, the mean number of days from the start of prophylaxis until study treatment was discontinued was 88.7 (95% CI: 80.6, 96.8) for VRZ and 71.5 (95% CI: 64.9, 78.2) for ITZ. Median values were 98.0 (range: 1, 258) and 70.0 (range: 3, 223) (Mann-Whitney p = 0.0026).

The reasons for unscheduled discontinuation of study treatment are summarized in Table 5.

The most frequently reported reason was AE: 67 subjects in the VRZ group and 57 subjects in the ITZ group. The number of subjects who indicated that they discontinued study medication because they did not tolerate their randomized treatment was larger for ITZ (48 subjects) than for VRZ (15 subjects).

Table 5. Study A1501073: Summary of Reasons for Unscheduled Discontinuation of Study Treatment - MITT Population

Reason	Voriconazole N=224	Itraconazole N=241
Breakthrough fungal infection	1 (0.8%)	4 (2.6%)
Non-compliance	5 (4.0%)	1 (0.7%)
Intolerance of study medication	15 (12.1%)	48 (31.4%)
Adverse event	67 (54.0%)	57 (37.3%)
Death	5 (4.0%)	3 (2.0%)
Subject completed at least 100 days but <180 days of prophylaxis	16 (12.9%)	18 (11.8%)
Other	15 (12.1%)	22 (14.4%)

Source: Table 13.4.8x
N is the number of subjects in the Modified Intent-to-Treat (MITT) Population for the given treatment group.
Percentages are calculated using the total number of valid non-missing reasons in the MITT Population for each treatment.
Any reason provided at a scheduled visit (ie, Visits 7, 8, or 9) is not summarized in this table.

There was a much higher rate of discontinuation of study treatment in the itraconazole treatment group due to Intolerance of study medication and overall lower number of days on treatment.

A total of 203 subjects (43.7%) used empirical therapy: 88 subjects (39.8%) in the VRZ group and 115 subjects (48.5%) in the ITZ group (difference in proportion: - 8.7%; p = 0.0598. An empirical therapy was defined as any additional antifungal medication (systemic or non-systemic) taken after the first dose of study medication for subjects who did not develop breakthrough proven or probable IFI. This calculation includes only the IFIs captured in the study database.

A total of 210 subjects (45.2%) used other antifungal agents as empirical or therapeutic treatment: 91 (40.6%) for VRZ and 119 (49.4%) for ITZ (difference in proportion: -8.8%; p = 0.0570). In this calculation, any subject with a breakthrough proven or probable IFI (as captured in the study database) was assumed to have received another antifungal agent (systemic or non-systemic) as a therapeutic treatment.

The mean number of days that subjects were inpatients in a hospital was 54.1 (95% CI: 50.1, 58.0) for VRZ and 57.2 (95% CI: 52.5, 61.9) for ITZ.

Mean scores for the effectiveness, convenience, and global satisfaction domains from the TSQM were higher at Visit 4 (Day 14) for VRZ compared with ITZ.

6.1.7.4. Results 1-year follow up

Follow-up of all subjects at 1 year after transplant was conducted by telephone in order to evaluate the survival rates for each treatment group. No formal safety assessments were performed.

Deaths that occurred up to and including 365 days after the first dose of study drug were included in the analysis. The difference in proportions (voriconazole – itraconazole) was calculated together with the 2-sided 95% confidence interval (CI) for this difference and corresponding p-value. An identical analysis was performed to evaluate mortality up to Day 400. For both analyses, Day 1 was defined as the first day of study medication; therefore, the first analysis strictly looked at survival at 1 year following the start of study medication rather than 1 year post transplant. Typically, a subject received their first dose of study treatment on the day of their transplant; however, some individuals started treatment a few days post transplant. In order to have Day 1 consistent across all analyses used in this study, Day 1 (in terms of first dose) was also used for the mortality analysis. This analysis used the modified intent-to-treat (MITT) population.

6.1.7.4.1. Analysis of survival at 1 year post transplant

The numbers of subjects who died within 1 year (i.e. until Day 365) were 58 (25.9%) in the VRZ group and 75 (31.1%) in the ITZ group. The difference between the 2 treatments was – 5.2% (95% CI: - 13.4%, 3.0%). The numbers of subjects who died within 400 days of transplant were 59 (26.3%) in the VRZ group and 76 (31.5%) in the ITZ group (difference= – 5.2%; 95% CI: - 13.5, 3.1).

6.2. Study A1501038

6.2.1. Study design:

Prospective, open-label, non-comparative, multicenter study for the secondary prophylaxis of IFI with voriconazole in patients with allogeneic stem cell transplants.

6.2.2. Study objectives:

6.2.2.1. Primary Objective

- To evaluate the efficacy of voriconazole as secondary prophylaxis on the rate of occurrence of proven and probable IFI in allogeneic SCT subjects having any underlying haematological disease with previous proven or probable IFI from the start of voriconazole prophylaxis until the 12-Month Follow-Up Visit

6.2.2.2. 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

- 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
- time to occurrence of proven/probable recurrent (same pathogen as previous IFI) IFIs from the start of voriconazole prophylaxis
- 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 survived free of IFI at 6 and 12 months after transplant
- the safety and tolerability of voriconazole as secondary prophylaxis after allogeneic SCT

6.2.3. Study methods:

Location: The study was conducted at 21 centres in 8 countries: Belgium (1), France (6), Germany (4), Portugal (1), Spain (4), Sweden (1), Switzerland (1), and United Kingdom (3).

Sample size: The sample size for this study was based on feasibility. With a sample size of 56 subjects, the 95% confidence interval limits of rate estimates would be ± 7.9%, ± 10.5% and ± 12.0% for IFI rates equal to 10%, 20% and 30% respectively. Assuming that approximately 10% of subjects would not be evaluable, it was planned that 63 subjects would be recruited into the study. The total number of subjects was not to have exceeded 70 subjects. Since it proved difficult to find a sufficient number of suitable subjects to enrol 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.

Study duration: The first subject visit happened on the 7th of February 2005, the last on the 4th of April 2008. 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.

6.2.3.1. Eligibility criteria/Study population:

Inclusion criteria were:

- Male and female subjects with previous proven or probable IFI in the previous 12 months, who were to be receiving an allogeneic SCT for any haematological disease
- Signed and dated informed consent was obtained from each subject in accordance with the local regulatory and legal requirements
- Females of childbearing potential had a negative serum β-HCG pregnancy test and were practicing an effective form of contraception
- Age ≥ 18 years

6.2.3.2. Exclusion criteria were:

- Pregnant or lactating women or women of childbearing potential not using an acceptable method of contraception
- Severe disease other than underlying condition, likely to jeopardize the planned termination of the study (e.g. acute myocardial infarction, unstable angina pectoris, potentially pro-arrhythmic conditions such as cardiac impairment due to previous cardiotoxic

chemotherapy, previous torsades de pointes, prolongation of the QT interval > 450 msec for men or > 470 msec for women)

- Abnormal screening findings considered by the investigator to be indicative of conditions that might affect study results (e.g. short bowel syndrome)
- Previous history of zygomycosis (e.g. Mucor, Absidia, Rhizopus)
- Positive serum galactomannan antigen test
- Active, symptomatic, uncontrolled IFI (persistence of clinical symptoms related to active fungal disease)
- Any evidence of active fungal disease as defined by the MSG-EORTC criteria; i.e. persistence of positive microbiological blood cultures or *Aspergillus* antigenemia, at time of enrolment (Visit 2)
- Present candiduria
- Previous failure of voriconazole in the treatment of IFI
- Concomitant use of voriconazole 36 hours before chemotherapy until at least 48 hours after chemotherapy
- Known intolerance to azole compounds
- Concomitant use of sirolimus, ergot alkaloids, terfenadine, astemizole, cisapride, pimozide, quinidine, carbamazepine, rifampicin, phenobarbital, ritonavir or efavirenz which might interfere with the evaluation of study drugs during the study specific systemic diseases
- Other medical conditions, including human immunodeficiency virus (HIV)-positive serology, that would interfere with the evaluation of the therapeutic response or safety of the study drug
- Alcohol and/or any other drug abuse
- Previous participation in this trial
- Abnormal laboratory test results, defined as impaired hepatic function, as shown by but not limited to transaminases, alkaline phosphatases, or bilirubin >5 x Upper Limit of Normal [ULN]
- Impaired renal function, as shown by but not limited to estimated creatinine clearance (Clcr) < 50 mL/minute (as per Cockroft-Gault formula)
- Any other condition which, in the investigator's judgment, could have increased the risk to the subject or decreased the chance of obtaining satisfactory data to achieve the objectives of the study
- Mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study and/or evidence of an uncooperative attitude
- Unable and/or unlikely to comprehend and/or follow the protocol
- Participation in any other studies involving investigational products, concomitantly or within 30 days prior to entry in the study
- Anticipated survival less than 72 hours

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

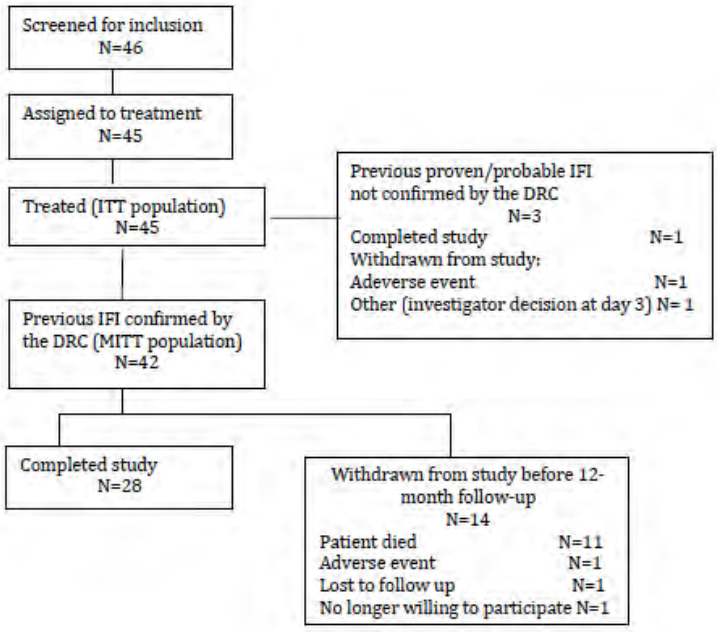
- subject was receiving prednisone (≥ 0.2 mg/kg), muromonab (OKT3), or mycophenolate mofetil
- antithymocyte globulin (ATG) or had received ATG within the 4 weeks before Day 100
- neutropenia (polymorphonuclear neutrophil leukocytes < 500/mm3) or had been neutropenic within the 10 days before Day 100

Depending on the subject's status, VRZ 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.

6.2.4. Patient disposition

This is shown in Figure 1.

Figure 1. Study AI501038 Patient disposition.



ITT, intent-to-treat; IFI, invasive fungal infection; DRC, data review committee; MITT, modified ITT

6.2.5. Demographics and baseline characteristics

For baseline demographics see Table 6.

Table 6. Study A1501038: 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

Source: Table 13.2.1
Abbreviations: N = number of subjects; SD = standard deviation

The majority of subjects (69%) had acute myeloid leukaemia as underlying disease. (Table 7).

Table 7. Study AI501038 Patients' baseline characteristics

Demographics	Patients (N=45)
Male, n (%)	28 (62)
Mean age (range), years	48 (22-72)
Mean body mass index (range)	24.6 (18.1-35.5)
Primary diagnosis, n.	
Acute myeloid leukemia	31
Acute lymphoblastic leukemia	7
Acute leukemia unspecified	3
Chronic myeloid leukemia transformation	2
Chronic lymphocytic leukemia	1
Mycosis fungoides	1

The history of previous IFI is depicted in Table 8. The most common was probably aspergillosis.

Table 8. Study A1501038: History of IFI previous to secondary VRZ prophylaxis

VORICONAZOLE (N=45)	Number (%) of subjects
Proven candidiasis	5 (11.40)
Proven aspergillosis	6 (13.60)
Probable aspergillosis	26 (59.10)
Proven other fungal pathogen	3 (6.80)
Probable other fungal pathogen	3 (6.80)
Missing fungal pathogen	1 (2.30)
Total	44 (97.80)

The majority of subjects (84%) received stem cell transplant (STC) from peripheral blood stem cells and unrelated donors (47%).

6.2.6. Duration of exposure to study drug

The median duration of treatment was 94 days (range 5-180 days) with 23 subjects receiving ≥ 91 days of treatment. Median of being in the study was 360 days after the start of VRZ prophylaxis (subject follow-up ranged from 5 - 469 days). Median durations, ranges, and most common duration category were similar for subjects in the MITT population, excluding the 2 subjects from one site.

6.2.7. Results

The efficacy analyses were based on the ITT, MITT, or PP population. The majority of analyses were based on a complete case analysis in which the outcome must be observed and/or the subject must be evaluable for the entire period of interest. This was considered a conservative approach.

6.2.7.1. Primary evaluations- proportion of subjects developing a proven or probable IFI:

For the primary efficacy evaluation, number of subjects developing IFI: a total of 3/28 (10.7%) [95% CI (2, 28)] patients had proven or probably IFI.

The respective fungal pathogens associated with each IFI were Candida albicans, Scedosporium prolificans and Zygomycetes. Two (2) of these 3 IFIs were relapses of a previous IFI.

6.2.7.2. Secondary evaluations:

Similar results were noted when examining the proportion of subjects developing a proven or probable IFI from the start of prophylaxis until the 12-Month Follow-Up Visit for the more PP Population: 13.0% (3 of 23 evaluable subjects with a 95% CI of 3 to 34%).

All demonstrated IFI occurred within the first 6 months (using complete cases).

For survival at the 12 month follow up: The crude survival rate, based on the number of subjects in the MITT population, was 80% at 180 days after the start of prophylaxis and 70% at 1 year after the start of prophylaxis.

Three of the 40 subjects (7.5%) in the MITT Population had an IFI post-transplant (based on the best case analysis and is not as conservative as the percentage based on a complete case analysis).

7. Clinical safety

7.1. Studies providing evaluable data

Safety data was submitted in Study A1501073, Study A1501038 and the periodic safety update report (PSUR) covering the period 1st of March 2010 to 28th of February 2011.

7.1.1. Study A1501073

All observed or volunteered adverse events (AEs) were recorded on the Case Report Form (CRF) form by the investigators and assessed by relationship to study drug according to the investigator's opinion. Serious AEs (SAEs) required immediate notification to Pfizer or its representative, from the time of providing informed consent to 28 calendar days after last administration of the investigational medication. Any serious AE afterward was to be reported if a causal association was suspected. Non serious AEs were to be reported up to 14 days after last administration of study medication.

An independent data safety monitoring board (DSMB) reviewed the safety of the study after 166 subjects had completed their prophylaxis. All reasons for discontinuation of prophylaxis were reviewed by the DSMB blinded as to study drug, including: suspected invasive fungal infection, causes of death, safety/intolerance (including SAEs).

7.1.2. Study A1501038

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) were to be reported. Serious AEs were recorded from obtaining informed consent to 28 calendar days after the last administration of the investigational product. If causal relationship was assumed any serious AE was to be reported regardless of time since last administration.

Adverse events (non-serious) were to be recorded from the time the subject has taken at least one dose of trial treatment through last subject visit. Each adverse event was to be assessed to determine if it met the criteria for serious adverse event. If a serious adverse event occurred, expedited reporting was to follow local and international regulations, as appropriate.

7.1.3. PSUR covering the period 1st of March 2010 to 28th of February 2011

This was the 11th PSUR for voriconazole since it was approved in the European Union (EU) on 19 March 2002. A new version of the voriconazole Core data Sheet (CDS) (28 March 2010) was issued during the PSUR reporting period. Worldwide, voriconazole has received marketing authorization in 99 countries and is currently marketed in 91 countries for the treatment of: invasive aspergillosis, candidemia in non-neutropenic patients, serious invasive *Candida* infections (including *C. krusei*), oesophageal candidiasis, serious fungal infections caused by *Scedosporium* spp. and *Fusarium*s pp., and other serious fungal infections in patients intolerant of, or refractory to, other therapy. Voriconazole is approved for the prevention of breakthrough of fungal infections in febrile high-risk patients (allogeneic bone marrow transplants, relapsed leukaemia patients).

It is estimated that more than 587,000 patients received voriconazole worldwide.

Between September and October 2010, the Marketing Authorization Holder (MAH) dispatched a Direct Healthcare Professional Letter to all EU countries' to inform them of the important new safety information relating to the potential risk of squamous cell carcinoma (SCC) associated with long term VFEND therapy, and appropriate preventative actions.

7.2. Extent of exposure

Study A1501073: Safety data was reported for the safety population using Pfizer Data Standards. The Safety population consisted of all subjects randomized to the study who received at least once the randomized study drug. Subjects from one site were excluded due to GMP issues from all efficacy analyses but were included in safety analyses. (MITT population, n= 234 in the voriconazole and n=255 in the itraconazole arm; follow up for 180 days and 1 year for death).

Study A1501038: 45 subjects participated in this observational study with a follow up of 12 months.

PSUR: Approximately 460 patients received voriconazole in MAH-sponsored clinical studies during this reporting period. The market experience for all voriconazole formulations distributed by the MAH during the reporting period is an estimate of the total patients on voriconazole. Patient estimates are based on voriconazole unit sales divided by the average daily dose and the average duration of therapy. The estimate was based on the assumption that all patients outside of the United States were treated using the same average dosage for the same average duration of time as patients in the major markets of Europe. During the reporting period, there were approximately 207,470 patients exposed to voriconazole in the United States, and 379,748 patients exposed to voriconazole in other countries.

One study comparing the safety, tolerability, and efficacy of voriconazole for primary therapy of invasive aspergillosis in paediatric was approved and five studies (evaluating voriconazole as primary therapy for aspergillosis and moulds, invasive Candida infections; drug use investigation; Vfend on scedosporiasis) were still ongoing during the study period; eight studies being completed or analysed during this PSUR period.

7.3. Safety results- Study A1501073

7.3.1. Adverse events

AEs were reported by 99.1% of the voriconazole group and 99.6% in the itraconazole group. Roughly half of subjects experienced AEs considered as related to treatment; 52.6% (123 subjects) in the voriconazole group and 54.5% (139 subjects) in the itraconazole group (for serious AE see respective section of this report). Severe AEs were reported for approximately half of all subjects in both the voriconazole (53.4%) and itraconazole groups (52.5%), but were infrequently considered related to treatment (13.7% and 12.2%, respectively).

The most frequently reported AEs in both treatment groups were pyrexia, mucosal inflammation, diarrhoea, nausea, and vomiting and were reported in proportions of subjects in the 2 treatment groups ranging from 33.8% to 56.1%; according to the sponsor those were associated with leukaemia or its treatment. The most common AE system organ classes for both treatment groups were gastrointestinal disorders and general disorders and administration site conditions.

A statistical analysis was performed for the incidence of treatment-emergent AEs (all causalities) per 30 days of study medication. The mean number of AEs per 30 days of treatment was 10.8 (95% CI: 8.7, 12.8) for voriconazole and 12.1 (95% CI: 10.1, 14.1) for itraconazole. The difference between the treatments was -1.4, favouring voriconazole, though this difference was not significant (p = 0.3423).

Treatment-related gastrointestinal disorders – specifically diarrhoea, nausea, and vomiting – occurred in higher proportions of subjects treated with itraconazole compared with voriconazole (Table 9). Treatment-related headache and rash were reported for similar proportions of subjects in both treatment groups. Adverse events associated with liver function – cytolytic hepatitis, hepatotoxicity, and abnormal liver function tests – were considered related to treatment in higher proportions of subjects in the voriconazole group compared with itraconazole. The eye disorder of visual impairment was considered related to voriconazole

treatment in 14 subjects (6.0%); no event of visual impairment was considered related to itraconazole treatment. All reported cases of visual impairment were mild to moderate in severity, non-serious, and resolved without sequelae.

Table 9. Study A1501073: Most frequently reported (10 or more subjects in a treatment group) treatment-related adverse events (Safety Population)

System Organ Class Preferred Term	Number (%) of Subjects	
	Voriconazole	Itraconazole
	N=234	N=255
Eye disorders		
Visual impairment	14 (6.0)	0
Gastrointestinal disorders		
Diarrhea	10 (4.3)	28 (11.0)
Nausea	18 (7.7)	38 (14.9)
Vomiting	9 (3.8)	40 (15.7)
Hepatobiliary disorders		
Cytolytic hepatitis	11 (4.7)	5 (2.0)
Hepatotoxicity	17 (7.3)	6 (2.4)
Investigations		
Liver function test abnormal	12 (5.1)	6 (2.4)
Nervous system disorders		
Headache	11 (4.7)	13 (5.1)
Skin and subcutaneous tissue disorders		
Rash	10 (4.3)	12 (4.7)

Source: Table 13.6.3.3.1
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 summarized.
Includes data up to 7 days after last dose of study drug.

The most common system organ class of treatment-related AEs in voriconazole subjects was hepatobiliary disorder (20.1%); the most common for itraconazole subjects was gastrointestinal disorder (32.2%) (Table 10).

Table 10. Study A1501073: Treatment-emergent adverse events (treatment related)

	VORICONAZOLE		ITRACONAZOLE	
	n	(%)	n	(%)
Number (%) of Subjects:				
Evaluable for adverse events	234		255	
With adverse events	123	(52.6)	139	(54.5)
Discontinued due to adverse events	60	(25.6)	55	(21.6)
Number (%) of Subjects with Adverse Events by System Organ Class:				
Blood and lymphatic system disorders	8	(3.4)	5	(2.0)
Cardiac disorders	6	(2.6)	2	(0.8)
Ear and labyrinth disorders	0		1	(0.4)
Endocrine disorders	1	(0.4)	0	
Eye disorders	28	(12.0)	7	(2.7)
Gastrointestinal disorders	29	(12.4)	82	(32.2)
General disorders and administration site conditions	16	(6.8)	25	(9.8)
Hepatobiliary disorders	47	(20.1)	28	(11.0)
Immune system disorders	1	(0.4)	2	(0.8)
Infections and infestations	8	(3.4)	11	(4.3)
Injury, poisoning and procedural complications	1	(0.4)	0	
Investigations	34	(14.5)	29	(11.4)
Metabolism and nutrition disorders	8	(3.4)	14	(5.5)
Musculoskeletal and connective tissue disorders	9	(3.8)	9	(3.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0		1	(0.4)
Nervous system disorders	15	(6.4)	15	(5.9)
Psychiatric disorders	17	(7.3)	4	(1.6)
Renal and urinary disorders	3	(1.3)	4	(1.6)
Reproductive system and breast disorders	1	(0.4)	6	(2.4)
Respiratory, thoracic and mediastinal disorders	13	(5.6)	13	(5.1)

Subjects are only counted once per treatment for each row.
Includes data up to 7 days after last dose of study drug.

For the incidence of treatment-related AEs per 30 days of study medication, the mean number of related AEs per 30 days of treatment was 1.6 (95% CI: 1.1, 2.2) for voriconazole and 1.9 (95% CI: 1.3, 2.5) for itraconazole.

7.3.1.1. Hepatobiliary adverse events

Overall, 87 subjects experienced AEs that were considered related to hepatobiliary investigations (increased levels in hepatic enzymes [AST, ALT, and gamma glutamyltransferase {GGT}] and bilirubin as well as other LFT abnormalities): 52 subjects (22.2%) in the VRZ and 35 subjects (13.7%) in the ITZ group. These events were considered related to treatment in 43 subjects in total: 27 subjects (11.5%) in the VRZ group and 16 subjects (6.3%) in the ITZ group.

There was no statistically significant difference in respect of the mean incidence of treatment-emergent all causality hepatobiliary investigations AEs per 30 days of study medication (0.2 for both groups).

7.3.2. Discontinuations

A total of 28 subjects discontinued from the study due to AEs: 15 subjects in the voriconazole group and 13 subjects in the itraconazole group. Of these, 15 subjects discontinued due to AEs considered related to treatment: 8 subjects in the voriconazole group and 7 subjects in the itraconazole group.

The incidence of discontinuation of study treatment due to AEs was similar for both treatment groups for both all-causality and treatment-related AEs (VRZ: 39.3% and 25.6%, respectively; ITZ: 39.6% and 21.6%, respectively). A similar trend was observed for the incidence of dose reductions and temporary discontinuations of study treatment for both all-causality and treatment-related AEs (VRZ: 19.2% and 9.4%, respectively; ITZ: 26.3% and 9.8%, respectively).

7.3.3. Deaths

A total of 87 subjects died up to and including Day 180: 40 subjects (17.1%) in the voriconazole group and 47 subjects (18.4%) in the itraconazole group (Table 11).

Table 11. Study A1501073: Summary of deaths up until day 180 by primary diagnosis- crude death rate-including deaths only recorded in the long term follow up pages and/or safety database

	VORICONAZOLE (N=234)	ITRACONAZOLE (N=255)
Number (%) of Subjects Who Died*	40 (17.1%)	47 (18.4%)
Number (%) of Subjects Who Died with the Following Primary Diagnosis [1]		
Acute Myeloid Leukaemia	16 (40.0%)	24 (51.1%)
Acute Lymphocytic Leukaemia	8 (20.0%)	3 (6.4%)
Myelodysplastic Syndrome	6 (15.0%)	7 (14.9%)
No Therapeutic Response	8 (20.0%)	11 (23.4%)
Chronic Myeloid Leukaemia Transformation	0	2 (4.3%)
Missing Primary Diagnosis	2 (5.0%)	0

N is the number of subjects in the Safety Population for the given treatment group.
*Percentages are calculated using N in the denominator.

7.3.4. Serious adverse events

An SAE was any untoward medical occurrence that resulted in death, was life-threatening (immediate risk of death), required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity or resulted in congenital anomaly/birth defect.

SAEs were reported for 47.4% (111) of subjects in the voriconazole and 37.3% (95) in the itraconazole group (including some that occurred after day 180); SAEs considered to be related to treatment occurred in 8.1% and 5.1% of subjects in the two groups.

Some 14 subjects had hepatobiliary disorders SAEs (6.0%) in the voriconazole group and 4 subjects (1.6%) in the itraconazole group. These were considered related to treatment for 9 subjects (3.8%) in the VRZ group and 2 subjects (0.8%) in the ITZ group. Results were similar for hepatobiliary investigations reported as SAEs.

7.3.5. Clinical laboratory evaluations

Laboratory evaluations consisted of haematology (Haemoglobin, haematocrit, white blood cell (WBC) count and differential count including neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets) and biochemistry (liver function test [LFT], renal function test and electrolytes) at repeated examinations throughout the study (screening [day - 6 to - 3], days 0, 14, 28, 56, 100, 140 and 180).

A total number of 221 subjects in the voriconazole group and 236 subjects in the itraconazole group were evaluable for laboratory abnormalities; of these, 214 subjects (97%) in the voriconazole group and 233 subjects (99%) in the itraconazole group had a laboratory value that met a criterion of possible concern. In both treatment groups, the most frequently reported clinical laboratory abnormalities without regard to baseline abnormality were associated with haematology parameters (Table 12). Abnormalities were observed less frequently in the liver function parameters total and direct bilirubin, and the electrolyte magnesium. However, increases in the liver enzymes were greater for voriconazole.

Table 12. Study A1501073: Most common (≥20% subjects) laboratory abnormalities (without regard to baseline abnormality) (safety population)

Parameter	Units	Criteria	Voriconazole n/N (%)	Itraconazole n/N (%)
Hemoglobin	g/dL	<0.8 x LLN	148/212 (70%)	175/230 (76%)
Hematocrit	%	<0.8 x LLN	153/212 (72%)	185/230 (80%)
Platelets	$10^3/mm^3$	<0.5 x LLN	122/209 (58%)	142/228 (62%)
WBC count	$10^3/mm^3$	<0.6 x LLN	151/209 (72%)	168/228 (74%)
Lymphocytes (Absolute)	$10^3/mm^3$	<0.8 x LLN	163/204 (80%)	186/218 (85%)
Total neutrophils (Absolute)	$10^3/mm^3$	<0.8 x LLN	126/204 (62%)	144/218 (66%)
Total bilirubin	mg/dL	>1.5 x ULN	49/221 (22%)	66/235 (28%)
Direct bilirubin	mg/dL	>1.5 x ULN	67/221 (30%)	72/235 (31%)
Magnesium	mg/dL	<0.9 x LLN	45/221 (20%)	61/235 (26%)

Source: Table 13.7.3.1

n = number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or during lag time.

N = total number of subjects with at least 1 observation of the given laboratory test while on study treatment or during lag time.

Abbreviations: LLN = lower limit of normal; ULN = upper limit of normal; WBC=white blood cell

Median changes from baseline laboratory values to last observation for haematology parameters were similar for both treatment groups (except platelets for which the increase was 3 times greater in voriconazole subjects).

7.3.6. Electrocardiograms

Table13 reflects findings of the performed electrocardiograms.

Table 13. Study A1501073: Summary of mean changes from baseline for electrocardiogram parameters (safety population)

		Voriconazole	Itraconazole
QT Interval (msec)			
Baseline	N	194	214
	Mean	367.0	370.2
	Min - Max	130 - 512	110 - 472
Visit 3	N	176	201
	Mean change	3.7	1.4
	SD	34.30	41.50
Visit 5	N	136	127
	Mean change	-2.4	17.6
	SD	48.20	48.27
QTc Interval (msec)			
Baseline	N	189	210
	Mean	412.7	411.9
	Min - Max	239 - 500	260 - 543
Visit 3	N	169	196
	Mean change	1.3	0.4
	SD	35.19	32.75
Visit 5	N	135	124
	Mean change	7.0	6.2
	SD	50.96	40.89

Source: Table 13.9.1
Baseline = Screening visit; QTc = QT interval corrected for heart rate; Min – Max = minimum and maximum values; SD = standard deviation
Means were determined within a subject prior to summarizing for all subjects.
Unplanned readings are included.

7.3.7. Graft Versus Host Disease

Some 102 subjects (43.6%) in the voriconazole group and 106 subjects (41.6%) in the itraconazole group experienced GvHD.

7.4. Safety results- Study A1501038

A total of 445 AEs were reported for all 45 subjects in the Safety population. A total of 26 subjects experienced 59 AEs considered related to treatment.

Two subjects discontinued from the study due to AEs, both of which were serious and considered related to treatment (hepatotoxicity and liver function test abnormal). Nineteen additional subjects permanently discontinued study medication due to AEs but were not discontinued from the study for this reason; AEs in12 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. Dose reductions or temporary discontinuations of study treatment due to treatment emergent AEs were reported for 7 subjects. In 2 of these subjects, at least 1 of these AEs was considered related to treatment.

The most common AEs were mucosal inflammation, diarrhoea, vomiting, pyrexia, headache and graft versus host disease (Table 14). The system organ classes with the most AEs were gastrointestinal disorders and general disorders and administration site conditions.

Table 14. Study A1501038: Most common adverse events (reported for >5 subjects) (Safety Population)

Preferred Term	N=45
Mucosal inflammation	17
Diarrhea	16
Vomiting	16
Pyrexia	15
Headache	14
Graft versus host disease	13
Hypertension	9
Abdominal pain	8
Febrile neutropenia	8
Thrombocytopenia	8
Anemia	7
Insomnia	7
Abdominal pain upper	6
Nausea	6
Rash	6

Source: Table 13.6.2.3
Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities
Note: MedDRA v11.0 used

The majority of AEs in this study were considered unrelated to treatment; 59 treatment-related AEs were reported for 26 subjects (Table 15). Most treatment- related AEs were mild or moderate in intensity. The most common treatment-related AEs were hepatotoxicity (4), hallucination (3) and headache (3). The most common treatment-related AEs were hepatobiliary disorders (11). Two subjects reported 3 treatment-related AEs of the eye disorders system organ class.

Table 15. Study A1501038: Treatment-emergent adverse events (treatment related)

	VORICONAZOLE
	n
Number of subjects:	
Subjects evaluable for adverse events	45
Number of adverse events	59
Subjects with adverse events	26
Subjects with serious adverse events	9
Subjects with severe adverse events	6
Subjects discontinued due to adverse events	14
Subjects with dose reduced or temporary discontinuation due to adverse events	2

Includes data up to 7 days after last dose of study drug.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.

Thirteen subjects died. Eleven subjects (24%) died during study participation between 48 and 326 days after start of prophylaxis. All deaths were due to causes unrelated to study medication and included relapse of leukaemia (5), respiratory failure or pneumopathy of unknown origin (3), GvHD (2), scedosporiosis in the setting of leukaemia relapse (1) and sepsis (1).

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 (2 subjects).

The most common clinical laboratory abnormalities without regard to baseline abnormality were associated with haematology parameters (platelets, WBC count, and absolute lymphocytes

and total neutrophils), liver function test parameters (direct bilirubin and ALT), and the electrolyte magnesium.

Thirty-nine subjects had at least 1 ECG recording. Ten subjects had 1 or more ECGs outside normal limits. Most ECG findings were of tachycardia and/or bradycardia.

7.5. Safety results- PSUR

No cases containing new safety information were identified in the current PSUR. Hepatobiliary events, neuropathies, vision-related events, multi-organ failure, coma, suicide, squamous cell carcinoma, skin cancer and cardiac failure were reviewed. As a result of these reviews, no issues were identified that change the benefit risk assessment of voriconazole.

7.5.1. Actions taken for safety reasons

Between September and October 2010, the MAH dispatched a Direct Healthcare Professional Letter to all EU countries' healthcare professionals to inform them of the important new safety information relating to the potential risk of squamous cell carcinoma (SCC) associated with long term VFEND therapy, and appropriate preventative actions.

7.5.2. Newly analysed studies during PSUR period:

There were two non-clinical studies (of which one was targeted safety study) and eight clinical studies analysed during the reporting period. None of the studies analysed during this reporting period contained important new safety information.

- Combination Subcutaneous and Oral (Gavage) Repeat-Dose Toxicity Study of PF-03910960 and UK-109496 in Juvenile Rats: The only finding attributed to administration of voriconazole (UK-109,496) was an increase in gamma glutamyltransferase (GGT) levels only in female rats. Based on these findings, administration of anidulafungin and voriconazole did not result in any increased toxicity when administered for 5 weeks at combined dosages as high as 10/30 mg/kg/day (voriconazole/anidulafungin). Based on the conclusions of this study, no new important findings that could alter the risk benefit assessment for voriconazole in humans were identified.

- **A1501067** Post marketing surveillance study to observe the safety and efficacy of Vfend i.v.; Phase IV study in Republic of Korea: This was an open-label non-interventional post marketing surveillance (PMS) study to determine the efficacy and safety in subjects who received the i.v. formulation of Vfend at any time during the treatment. In total, there were 692 subjects enrolled. Of these, 379 subjects were treated with the i.v. formulation of Vfend only, and 313 subjects were treated with Vfend tablets also. In total, 119 subjects discontinued due to AEs. Only for a minor proportion of subjects, the AEs leading to discontinuation were assessed as related to study treatment. Frequently reported AEs leading to discontinuation as well as SAEs with fatal or non-fatal outcome were sepsis or septic shock, leukaemia, disease progression, multi-organ failure and pneumonia. Most of these were not assessed as treatment related. SAEs with fatal or non-fatal outcome that were assessed as treatment related were most commonly septic shock or sepsis, renal failure and disease progression. The type and features of these events are consistent with the known safety profile of Vfend.

- **A1501068** Post marketing surveillance study to observe the safety and efficacy of Vfend tablets. Phase IV study in Republic of Korea: This was an open-label non-interventional PMS study to determine the efficacy and safety in 543 subjects who received the tablet formulation of Vfend at any time during the treatment with voriconazole. In total, 53 subjects discontinued due to AEs. For almost half of the subjects, the AEs leading to discontinuation were assessed as related to study treatment. Twenty-nine subjects who discontinued died. The number of subjects who died was 83. The majority of deaths were

assessed as non-treatment related. There were 14 subjects with fatal SAEs [cardiac arrest, cardiogenic shock, death, disseminated intravascular coagulation, liver function test abnormal, pneumonia, pulmonary haemorrhage, renal failure acute, sepsis, septic shock] assessed as treatment related by the investigator. None of the AEs reported occurred in more than 4.1% of the subjects. Frequently reported AEs leading to discontinuation as well as SAEs with fatal or non-fatal outcome were sepsis/septic shock, leukaemia and pneumonia caused by underlying disease. The type and features of these events are consistent with the known safety profile of voriconazole.

- **A1501081** An open-label, intravenous to oral switch, multiple dose study to evaluate the pharmacokinetics, safety and tolerability of voriconazole in immunocompromised adolescents aged 12 to <17 years who are at high risk for systemic fungal infection. Phase 2 study in United States. Twenty-six subjects were assigned to treatment. Twenty-six subjects were treated with voriconazole IV and 22 were able to switch to oral voriconazole. Twenty-one of these subjects completed the study. The safety and tolerability of voriconazole in adolescents during both IV and oral administration were consistent with the known safety profile of voriconazole.

- **A1501082** Voriconazole in high-risk patients with invasive fungal infections in Slovakia. An open, prospective, non-comparative phase 4 study: This was a non-interventional, prospective, open-label study in which subjects received treatment with the drug under study while continuing to take their indicated concomitant medication. A total of 174 subjects were assessed for clinical and/or mycological efficacy at the end-of-treatment (EOT) visit. Of the subjects who were assessed for clinical efficacy, the majority experienced clinical cure (64 [36.2%] subjects) or clinical improvement (64 [36.2%] subjects) and 36 subjects (20.3%) experienced no clinical cure. Of the subjects who were assessed for mycological efficacy, 34 (19.2%) subjects experienced mycological cure and 10 (5.6%) subjects experienced no mycological cure. A total of 174 (98.3%) subjects were assessed for the tolerability of voriconazole at the EOT visit. In the majority of subjects, the tolerability of voriconazole was assessed as 'very good' [59.3%] or 'good' [34.5%]. The tolerability of voriconazole was assessed as 'moderate' in 8 (4.5%) subjects and as 'poor' in no subject. Forty-two subjects had SAEs during the study and 35 (19.8%) subjects had severe AEs. Eleven (6.2%) subjects discontinued the study as a result of AEs. All subjects with SAEs died. A total of 42 subjects died during the study. Most deaths were attributable to the underlying conditions. One subject had a fatal event of sudden death that was considered to be related to study treatment by the sponsor. Only one SAE (toxic nephropathy in one subject) was considered related to study treatment. The deaths reported during this study were consistent with those usually expected in the study population under investigation.

- **A1501088** A Phase 2, open-label, intravenous to oral switch, multiple dose study undertaken in the US to evaluate the pharmacokinetics, safety and tolerability of voriconazole in immunocompromised children aged 2 to < 12 years who are at high risk for systemic fungal infection. 40 were treated with voriconazole i.v. and 34 subjects were able to switch to oral voriconazole. 31 of these subjects completed the study. 6 subjects discontinued voriconazole i.v. treatment due to AEs (4 related to study drug). The safety and tolerability of voriconazole in children during both IV and oral administration were consistent with the known safety profile of voriconazole.

- **A8851011** Phase IV open-label non-comparative study conducted in the WS and Republic of Korea of IV anidulafungin followed by oral azole therapy for the treatment of candidemia and invasive candidiasis. Twelve adverse events were considered voriconazole-related [nausea, vomiting (2), chest discomfort, drug hypersensitivity, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, blood alkaline phosphatase increased, international normalised ratio increased, confusional state, drug eruption, and rash]. A regimen of IV anidulafungin followed by oral voriconazole or fluconazole appeared to be

safe and well-tolerated during this study. The safety profile of these agents was similar to what has been reported in other studies for treating subjects with candidemia/invasive candidiasis.

- **A8851015** A Phase 4, open-label, non-comparative, study conducted in South America of intravenous anidulafungin, followed optionally by oral voriconazole, for treatment of documented candidemia / invasive candidiasis in hospitalized patients. The planned sample size was 210 subjects, but only 54 subjects were screened and randomized due to slow enrolment. Due to the small sample size, the results of the global response subgroup analyses were inconclusive. No relevant safety conclusions were provided for voriconazole.
- **A8851019** Open-label, non-comparative, study of intravenous anidulafungin, followed optionally by oral voriconazole or fluconazole therapy, for treatment of documented candidemia/invasive candidiasis in intensive care unit patient population. Phase 3b study in 19 countries: In the mITT population, 112 subjects (65.9%) only received i.v. anidulafungin as study drug. The remaining subjects were administered an oral azole following anidulafungin as part of their treatment regimen; 44 subjects (25.9%) received fluconazole and 14 subjects (8.2%) received voriconazole. One patient experienced 2 non-serious events (increased aspartate aminotransferase and increased blood alkaline phosphatase) considered voriconazole-related.

7.5.3. Newly published studies during PSUR period

- Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. Cordonnier C, Rovira M, Maertens J, *et al*. *Haematologica* 2010;95(10):1762-8. Essentially reporting the findings of Study A1501038.
- Species distribution and antifungal susceptibilities of yeast clinical isolates from three hospitals in Korea, 2001 to 2007. Lee MK, Yong D, Kim M, *et al*. *Korean J Lab Med* 2010;30(4):364-72.Reported that *Candida albicans* was the most frequent isolate but identified an increasing share of non-*albicans Candida* and non-*Candida* yeasts.
- Long-term visual safety of voriconazole in adult patients with paracoccidioidomycosis. Laties AM, Fraunfelder FT, Tomaszewski K *et al*. *Clinical Therapeutics* 2010;32(13):2201-17. Clinical assessment in this study (n=35) found no evidence of an effect of voriconazole on long-term visual function in these adult patients with paracoccidioidomycosis.
- Effects of erythromycin on voriconazole pharmacokinetics and association with CYP2C19 polymorphism. Shi HY, Yan J, Zhu WH, *et al. Eur J Clin Pharmacol* 2010;66(11):1131-6. Both CYP2C19 genotypes and CYP3A4 inhibitor erythromycin can influence the plasma concentration of voriconazole, and erythromycin increases plasma concentration of voriconazole in a CYP2C19 genotype-dependent manner.

7.5.4. Targeted safety studies during PSUR period

Combination subcutaneous and oral dosage-range repeat-dose toxicity study of anidulafungin and voriconazole in juvenile rats. Anidulafungin was well tolerated in juvenile rats following repeated dosing for approximately two weeks. Combined dosages of anidulafungin and voriconazole, as well as voriconazole without co-administration of anidulafungin reduced body weight gains in both sexes during the entire dosage period and increased liver weights at the end of the dosage period. The study results did not reveal any new relevant safety data.

7.5.5. Efficacy-related information:

During the current reporting period there were 33 cases (65 events) that coded to MedDRA Preferred Terms (PTs) potentially indicative of lack of efficacy, representing 4.3 % of the overall dataset, compared to a reporting rate of 3.8 % in the previous PSUR. Results did not highlight any specific increasing trend in lack of efficacy/resistance since the launch of voriconazole.

7.5.6. Overall PSUR safety evaluation by sponsor:

A total of 773 medically confirmed serious spontaneous, non-serious spontaneous and solicited serious, related cases (containing 1, 393 events) fulfilled criteria for inclusion in this one-year safety update report, including 144 cases containing only non-serious listed (NSL) events (173).

This PSUR presents an analysis and discussion for all medically confirmed cases as a single dataset. Prior PSURs separated out the analysis and discussion of non-serious listed cases. For this reason, the reporting proportions for this dataset may have increased.

7.5.6.1. Unlisted adverse events

No unlisted events were reported with a reporting rate ≥ 2% during this one-year-period.

7.5.6.2. Listed adverse events:

The most commonly reported (≥ 2%) listed AEs during this reporting period were Hallucination (44 cases, 5.7%), Visual impairment (44 cases, 5.7%) Hepatic function abnormal (43 cases, 5.6%), Photophobia (39 cases, 5.0%), Photosensitivity reaction (32 cases, 4.1%), Drug level increased (26 cases, 3.4%), Drug ineffective (25 cases, 3.2%), Liver function test abnormal (24 cases, 3.1%), Vision blurred (24 cases, 3.1%), Alanine aminotransferase increased (19 cases, 2.5%), Liver disorder (18 cases, 2.3%), Hallucination visual (17 cases, 2.2%), Cholestasis (16 cases, 2.1%).

7.5.6.3. Comparison with previous PSUR:

Overall, the pattern of adverse event reporting was similar, with increases noted in the SOCs.

Eye disorders (RR= 1.6) and Musculoskeletal disorders (RR=2.0). All the events are listed or compatible with the listed events and the increase in the reporting period could be attributed to the inclusion of NSL cases in the overall dataset. None of these events were reported in > 2% of all cases and no safety concerns have been identified upon review of these cases.

7.5.6.4. Hepatobiliary Events:

During the current reporting period, there were 173 cases containing relevant hepatobiliary events. The majority of cases was serious (136 cases, 79%) and reported listed events (96%).

Patients were reported as recovered/recovering from hepatobiliary events in 62% of cases while 1 case reported acute hepatic failure which contributed to the fatal outcome. A review of the 2 cases reporting unlisted hepatobiliary events was not suggestive of any new safety concerns. Based on this review, no changes to the CDS (core data sheet) are warranted at this time; however, these events will be reviewed and discussed in the next PSUR.

The University of Wisconsin Hepatic Education Programme was initiated in Nov 2009, during the PSUR 10 reporting period. As the reporting rate during the current PSUR 11 is comparable to that of PSUR 10, there appears to be little impact of the Education Programme on the reporting of hepatic-related adverse events. Depending on the extent of participation during current year, the MAH will re-evaluate the suitability of this educational program as an effective risk minimization activity, and propose additional activities as appropriate.

7.5.6.5. Neuropathy peripheral:

During the reporting period, there were a total of 21 cases reporting MedDRA PTs of the Neuropathy peripheral. Upon review, 12 cases contained limited information; thus preventing a meaningful assessment of causality. One case reported a listed event (Guillain-Barre syndrome). In the remaining cases, causality could not be completely excluded based on temporality; however positive dechallenge was reported in only 2 cases. Upon review of these cases, no new significant safety concern was identified. No changes to the CDS are warranted at this time.

7.5.6.6. Vision-related events:

During the current reporting period, there were 128 cases reporting 291 relevant vision-related events. The most commonly reported visual events were Visual impairment, Photophobia, Vision blurred, chromatopsia, xanthopsia, Colour blindness acquired, Photopsia and Visual acuity reduced; these events are all listed or consistent with the CDS. The majority of the cases (117) reported events that are listed or consistent with listed events, non-serious, or transient. Upon review of the remaining 11 cases, no new safety information was identified that would alter the risk-benefit profile of voriconazole. No changes to the CDS are deemed necessary at this time.

7.5.6.7. Multi-organ failure:

During the current reporting period, there were 4 case reports of multi-organ failure. In 2 of the 3 spontaneous reports, the patients had significant co-morbid conditions (cancer, septic shock) which contributed to the event. In the 3rd spontaneous report, the patient developed multi-organ failure 2 years after voriconazole therapy was discontinued. In the remaining report, the patient also had significant medical history and the event of multi-organ failure was considered not related to voriconazole therapy. Upon review of these cases, no new safety issue was identified that would warrant a change to the CDS.

7.5.6.8. Coma:

The data provided in these two cases are not indicative of a causal association between voriconazole treatment *per se* and coma. In the first case, a possible drug interaction between voriconazole and oxycodone appears to have contributed to development of coma. The second case contains limited information to allow determination of a causal association with voriconazole.

7.5.6.9. Suicide:

One case was identified during this period involving a 75-year old female with significant co-morbidities and numerous other medications. No changes to the CDS are deemed necessary based on review of this case.

7.5.6.10. Skin cancer:

The search identified 10 reports including one fatal report. All reports spontaneous and were received from the following countries: United States (8), and one each from Australia and the United Kingdom. All reports from the United States were all received from the same physician, contained limited information involving patients ranging from 34 to 71 years of age with a mean of 53 years; 6 of the 8 reports as male (5) and female (1). In all 8 cases patients had a history of lung transplant and developed skin cancer while receiving voriconazole therapy. Therapy dates, dosage, concomitant medications, event onset and event outcome were not provided in any of the reports. In one of the remaining 2 reports, the patient had a history of skin cancer and was at high risk of developing further cancers. In the last report, it was reported that the patient had an unspecified skin disorder prior to initiating voriconazole therapy. Voriconazole has been associated with photosensitivity skin reaction. In addition, the patient was also taking concomitant medications known to cause increased sensitivity to the sun. The information provided in these last 2 cases is inconclusive for a potential association between voriconazole and skin cancer. Information has been added to the CDS to inform prescribers of the potential association between long-term voriconazole treatment and the development of SCC of the skin and melanoma.

7.5.6.11. Squamous cell carcinoma:

The search identified 6 reports; all were received from spontaneous sources, including three from literature sources. Reports were received from the following countries: France (n=3); the United States (n=2), and Japan (n=1).Voriconazole has been associated with photosensitivity

skin reactions; however, most of the patients had multiple risk factors and underlying conditions.

(immunosuppressive therapy, photosensitivity, prior history of skin cancer) which made them more susceptible to the development of squamous cell carcinoma. Information has been added to the CDS to inform prescribers of the potential association between long-term voriconazole treatment and the development of SCC.

7.5.6.12. Death:

During the current reporting period, there were 71 cases reporting fatal outcomes. In 21 cases the patients died for reasons other than the reported events. Twenty-one cases contained limited information either globally or regarding the fatal outcomes, which did not allow meaningful assessments as to the potential relationship between a possible drug-induced adverse event and the patient's demise. In 15 cases, the cause of death or the event(s) that contributed to death were either considered unrelated to voriconazole by the reporter/Investigator or were due to progression of pre-existing illness or other disorders. In 14 cases, including 7 cases where the fatal AE/outcome was attributed to a lack of effect, a role of voriconazole in determining the onset of an AE that caused or contributed to the fatal outcome could not be completely excluded; however, most patients had concurrent disorders or received other medications that could have led to the adverse events or the fatal outcome.

7.5.6.13. Long-term use:

Long-term voriconazole treatment (>90 days) was reported in 32 cases. No new safety information was identified upon review of these cases. No changes to the CDS regarding long-term treatment are warranted at this time.

8. Clinical questions and responses

8.1. Efficacy

8.1.1. Study A1501073

8.1.1.1. Question 1:

What is the potential impact of empirical antifungal therapy administered concomitantly to the study medication? Apparently, the higher proportion receiving empirical therapy in the itraconazole arm is supposed to underline the higher need for other anti-fungal treatment in this group. However, the protocols for empirical therapy might vary between centres/countries as might have the duration (number of days on empirical therapy) between the groups. Is it possible that empirical therapy prevented the development of IFI differently between the two groups, hence introduced confounding?

8.1.1.1.1. Pfizer response:

The investigators did not collect information regarding the protocols for empirical therapy. Some of the non-study drug antifungal agents were given as continued prophylaxis after randomised study drug was discontinued and others were more likely used for empirical therapy and/or treatment of suspected IFI. Review of the non-study systemic antifungals is summarised in Table 16. The most likely of these to be given as empirical therapy for treatment of suspected IRIs were caspofungin and amphotericin (liposomal or conventional).

Table 16. Comparison of non-study systemic antifungals

Systemic antifungal agent	Voriconazole (n=224)	Itraconazole (n=241)
Caspofungin	24 (10.7%)	48 (19.9%)
Liposomal amphotericin	14 (6.3%)	17 (7.1%)
Conventional amphotericin B	4 (1.8%)	7 (2.9%)
Fluconazole	21 (9.4%)	37 (15.4%)
Itraconazole	5 (2.2%)	8 (3.3%)
Voriconazole	9 (4.0 %)	34 (14.1%)
Posaconazole	5 (2.2%)	11 (4.6%)

8.1.1.1.2. Evaluator comment

While conceding the difficulty faced in management of highly immune compromised patients, and the necessity to treat each case on its merits, in the absence of recorded information or protocol mandated management strategy, confounding could not be ruled out.

8.1.1.2. Question 2:

Despite the fact that many other publications applied a similar concept in respect of allowing for empirical therapy, Cornely et al. defined failure as 'receipt of any other systemic antifungal agent for 4 days or more', an approach that appears to be more conservative. How would you assess the impact of empirical therapy in light of these factors?

8.1.1.2.1. Pfizer response

If patients who received any other systemic antifungal agent for 4 days or more were considered to be failures, the success rate at day 180 would be 37.5% (84/224) for voriconazole and 24.9% (60/241) for itraconazole with difference 12.6% [95% CI (4.2% to 21.0%)] still considered significant. (Though not accounting for multiplicity.)

8.1.1.3. Question 3:

Please clarify the definition of insufficient prophylaxis and discontinuation:

- *The numbers for success of prophylaxis at day 100 are reported with 121(54.0%) in the voriconazole and 96 (39.8%) in the itraconazole group; whereas the numbers for insufficient prophylaxis are 104 (46.4%) in the voriconazole group and 147 (61.0%) in the itraconazole group. Should not be the sum 100%, respectively 224 and 241 for the two groups (of minor concern!)?*
- *Table 5 in Module 5 (clinical study report) shows the disposition of subjects. The numbers of subjects who discontinued from the study before day 180 are divided into different (and relevant) categories.*
  - What is the meaning of failure of prophylaxis in contrast to IFI?
  - The category "Other reasons" contains the proportion of subjects who took empirical therapy for more than 14 days- please provide a similar table for insufficient prophylaxis at day 100 (the report states on insufficient prophylaxis "ie, who missed more than 14 days of prophylaxis before Visit 7, took less than 86 days of prophylaxis before Visit 7, or, if randomized to itraconazole, took more than 14 days of itraconazole capsules before Visit 7"). Does this statement include insufficient prophylaxis due to AE, death, empirical therapy, etc? Please provide stratification by reasons that led to discontinuation of prophylaxis until day 100.
  - Another conclusion drawn from table 5 [of the CSR] is potential for the presence of bias. The proportion of subjects not willing to continue the study seems higher

(significantly?) in the itraconazole group- considering the non-blinded design an indicator for bias?

8.1.1.3.1. Pfizer response

Two patients in each group were considered successes at day 100 but were categorised as receiving "insufficient prophylaxis" for receiving less that 86 days of study drug before day 100. One patient was considered a failure at day 100 because voriconazle was discontinued for hepatic toxicity. There were two cases that were permanently discontinued from the study because of "failure of prophylaxis" according to the investigator: One patient prematurely discontinued voriconazole after 26 days because of "intolerance of study medication", and one patient discontinued itraconazole after 16 days because of a possible IFI that was not confirmed to be proven or probable.

Twelve patients in the itraconazole group and 2 patients in the voriconazole group withdrew for reported reason "subject no longer willing to participate in study". One patient in the itraconazole group discontinued during the post-study treatment phase. The remaining patients discontinued the study at the time they discontinued study drug. In the voriconazole group, 1 patient discontinued study drug because of "ongoing nausea", and the other withdrew consent. In the itraconazole group, 3 patients discontinued because of intolerance of study medication, 2 because of adverse events, and the remaining 5 withdrew consent. We do not believe that these findings indicate potential bias.

The investigator-assessed reasons for discontinuation of study drug prophylaxis prior to day 100 are listed in Table 17 below:

Table 17. Investigator-Assessed Reasons for Discontinuation of Study Drug Prophylaxis Prior to Day 100

Reason	Voriconazole n=224	Itraconazole n=241
Breakthrough fungal infection	1	4
Non-compliance	3	1
Intolerance of study medication	15	52
Adverse event	67	56
Death	4	2
Subject completed at least 100 days but < 180 days of prophylaxis	1	2
Other	11	26

8.1.1.3.2. Evaluator comment

Table 17 above includes "Subject completed at least 100 days but < 180 days of prophylaxis" which is out of place in a list of reasons for discontinuation before Day 100. The table highlights the discrepancies between groups in reasons for discontinuation with many more patients in the itraconazole group discontinuing for intolerance of study medication and "other" than in the voriconazole. The large numbers of discontinuations are considered to have the potential to bias results.

8.1.1.4. Question 4.

Is it possible, respectively how likely, that the non-blinded design is a potential source for bias- especially when the main finding is based on a difference in duration of taking the study medication (which could be influenced by the non-blinded design rather easily)?

8.1.1.4.1. Pfizer response

If blinding were to be undertaken, patients would have an added burden of treatment and would have included a placebo containing cyclodextrin which has a recognised tolerability profile. A placebo containing cyclodextrin would have impaired the ability to compare long-term tolerability which is an important consideration given the prolonged period of risk for IFI.

8.1.1.4.2. Evaluator comment

Regarding questions 3 and 4 and with respect to participants' willingness to continue, and also the duration of taking the medicine, in an unblinded study the possibility of bias due to an unpalatable treatment in one arm could not be ruled out.

8.1.1.5. Question 5:

Characteristics of subjects in the two study groups don't differ significantly, however there are more men and the prevailing ethnicity is white. Are these results generalizable to other/general HSCT populations?

8.1.1.5.1. Pfizer response

The distribution of gender and race was similar to that of other studies.[1] The belief is that there were adequate numbers of females and non-whites to allow generalisation to other/general HSCT population.

8.1.1.6. Question 6:

What is the explanation for the low IFI rates in this study? Does this low rate pose a limitation to the estimation of an IFI-preventing effect of voriconazole versus itraconazole?

8.1.1.6.1. Pfizer response

One reason for the low IFI rate could be that both study drugs are active against Aspergillus. The majority of the IFI's in the other studies were cases of IA that developed in patients receiving fluconazole as prophylaxis.

Another reason for the low rate of IFI's in our study is that we used the 2002 European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) definitions which include proven or probable IFI In fact, the use of these definitions for antifungal prophylaxis trials has recently been questioned (Wingard *et al*, 2010). The reason is that in a patient with a suspected IFI, investigators are likely to discontinue study drug prophylaxis before a proven or probable diagnosis of IFI can be confirmed.

We organized a second Data Review Committee (DRC) to re-examine the reasons for study drug discontinuation in this study. This DRC reviewed patient data blinded to study drug and assigned a primary reason for study drug discontinuation to each case. In this review, the definitions for IFI's were broadened to include proven, probable and possible IFI according to the 2008 EORTC/MSG definitions.

- Proven IFI – clinical signs and symptoms, radiological finding c/w IFI, and mycological or histopathological confirmation of IFI from a biopsy
- Probable IFI – clinical signs and symptoms, radiological finding c/w IFI, and one microbiological criterion (either mycology or serology)
- Possible IFI – clinical signs and symptoms, radiological finding c/w aspergillosis, without a microbiological criterion (either mycology or serology)

[1] Wingard *et al*. Randomized, double-blind trial of fluconazole verseus voriconazole for prevention of invasive fungal infection after allogenic hematopoietic cell transplantation. *Blood*. 2010;116(24):5222 – 5118
Ulmann *et al.* Posaconazole or fluconazole for prophylaxis in severe graft-versus-host-disease. *NEJM*. 2007;356 (4):335 - 47

- Suspected IFI – clinical signs and symptoms, with report of pulmonary disease c/w IFI, but without report of a radiological finding and without a microbiological criterion
- Persistent fever with no evidence of IFI – persistent fever, typically in the context of prolonged neutropenia, without report of pulmonary disease

The data for all remaining patients who prematurely discontinued study drug were also reviewed by the DRC and assigned a primary reason for study drug discontinuation using the following categories: gastrointestinal intolerance, LFT abnormality, visual toxicity, other drug toxicity, progression of underlying disease, other medical condition, other reason not specified above.

The DRC-assessed reasons for study drug discontinuation are listed in Table 18. We believe that these data provide a better estimation of the IFI-preventing effect of voriconazole compared to itraconazole. These data were recently presented at an international medical conference.[2]

Table 18. Number (%) of Patients Who Discontinued Study Drug, by Primary Reason

Reason	Voriconazole n (%)	Itraconazole n (%)	p value
	n=104*	n=147*	
Probable IFI	1 (1.0)	4 (2.7)	NS
Possible IFI	1 (1.0)	14 (9.5)	<0.01
Probable or Possible IFI	2 (1.9)	18 (12.2)	<0.01
Suspected IFI	3 (2.9)	0 (0.0)	NS
Persistent fever w/o evidence IFI	5 (4.8)	11 (7.5)	NS
Any IFI-related reason	10 (9.6)	29 (19.7)	<0.05
Gastrointestinal intolerance	4 (3.8)	45 (30.6)	<0.001
LFT abnormality	45 (43.3)	15 (10.2)	<0.001
Visual toxicity	6 (5.8)	0 (0.0)	<0.01
Other drug toxicity	3 (2.9)	1 (0.7)	NS
Progression of underlying disease	5 (4.8)	2 (1.4)	NS
Other medical condition	20 (19.2)	26 (17.7)	NS
Other reason / unable to assess	11 (10.6)	29 (19.7)	NS

Abbreviations: IFI = invasive fungal infection; LFT = liver function test; NS = not significant.

* Number of patients who discontinued study.

8.1.1.6.2. Evaluator comment

With respect to "Probable or Possible IFI", the p-value for the latter is heavily weighted by the results for Possible IFI and in neither case is multiplicity considered. Thus these results are considered hypothesis generating.

8.1.1.7. Question 7:

Another factor recommended for the prevention of IFI is the attempt to reduce the exposure to moulds. Guidelines for the treatment of HSCT recipients (Tomblyn et al.; Biol

[2] Bow EJ, Cornely OA, Slavin M, et al. Recategorisation of reasons for premature discontinuation of antifungal prophylaxis in the IMPROVIT study – focus on IFI-related reasons. Poster presented at the 22nd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), London, UK, 31 March – 3 April 2012

Blood Marrow Transplant 15: 1143-1238) suggest that recipients at risk should stay in HEPA airflow equipped facilities. Has exposure in the participating centres been assessed?

8.1.1.7.1. Pfizer Response

This information was not collected.

8.1.1.8. Question 8:

Appendix 10.1.1x introduces an interesting question: the size of the observed effect seems to be quite heterogeneously between different countries. For instance, the coefficient for Spain is -0.61 (~OR=0.25) whereas the coefficient for the Czech Republic is 0.98 (~OR=9.5). Is it correct to present pooled data; respectively, does "country" act as an effect-modifier?

8.1.1.8.1. Pfizer response

We regenerated the logistic model by including an interaction term of "treatment by country". The interaction was not significant (p = 0.61). In the absence of effect-modification, an estimate of treatment effect by pooling across countries is generally valid.

8.1.1.9. Question 9:

Why was itraconazole considered as most suitable comparator instead of other medications, such as posaconazole?

- *Cornely et al. compared posaconazole versus flucon- or itraconazole (admittedly not in the same patient population) and found that 'posaconazole prevented invasive fungal infections more effectively than did either fluconazole or itraconazole and improved overall survival.' These results have been supported by a recently published study (which came admittedly too late for your trial) by Sánchez-Ortega et al. Bone Marrow Transplant. 2011 May; 46(5):733-9 (small sample size though: 'Our single-centre experience suggests that antifungal prophylaxis with posaconazole may lead to a better outcome than itraconazole for patients in the early high-risk neutropenic period after allogeneic BMT.'*
- *If the age-limitation of posaconazole to patients>13 years was a concern it is noted that the number of subjects below the age of 13 years who were included in Study A1501073 is almost negligible.*

8.1.1.9.1. Pfizer response

At the time the study was designed, posaconazole was still investigational and fluconazole was the only oral agent approved for prophylaxis in all HSCT recipients. Itraconazole is a broard-spectrum antifungal with activity against a wide range of yeasts and filamentous fungi, including *Candida* and *Aspergilllus* species and has proven efficacy in the treatment of invasive infections with these organisms.

There was strong data to support the efficacy of itraconazole compared to fluconazole as prophylaxis against this infection in allo HSCT patients:

- In a meta-analysis of 13 randomized clinical trials, itraconazole prophylaxis significantly reduced incidence of IFI, and the oral solution was superior to the capsule in reducing IFI incidence and mortality (Glasmacher *et al*, 2003).
- Subsequent studies also showed a reduction in the incidence of aspergillosis with itraconazole prophylaxis in allo HSCT recipients (Grigg *et al*, 2004; Marr *et al*, 2004).
- In a prospective randomized clinical trial, itraconazole was demonstrated to be superior to fluconazole in preventing IFI in allo HSCTs (Winston *et al*, 2003). At the time we conducted the study itraconazole was approved for prophylaxis in most European countries, and was one of the drugs of choice for this indication.

At the time we conducted the study itraconazole was approved for prophylaxis in most European countries, and was one of the drugs of choice for this indication. Itraconazole was available in three formulations: oral solution, capsules, and IV. The oral solution of itraconazole was chosen as the main comparator for this study because it is more reliably absorbed than the capsule formulation. Although the oral solution of itraconazole is associated with nausea, unpleasant taste and diarrhoea, the protocol included strategies to maximize the chance that patients could complete the planned duration of prophylaxis:

- Patients with mucositis could be switched to the intravenous formulation of itraconazole at any time during the study. We provided clinical supplies of the intravenous formulation of itraconazole for sites in countries where it was not commercially available.
- Patients who were unwilling to continue the oral solution were permitted to take itraconazole capsules for a maximum of 14 days without being considered to be failures.

8.1.1.10. Question 10:

The study population was limited to a few indications for HSCT (acute leukaemia or myelodysplastic syndrome, failure of therapy for lymphoma or transformation of chronic myeloid leukaemia). Are the results transferrable to patients who receive HSCT due to other underlying diseases, such as aplastic anaemia and others?

8.1.1.10.1. Pfizer response

We believe that the results of the study apply only to the patient population studied.

8.1.1.11. Question 11:

Are these results transferrable to other populations at risk for IFI which are neither explicitly included nor excluded by the proposed PI, such as solid organ recipients?

8.1.1.11.1. Pfizer response

We do not believe that the results of this study are applicable to recipients of other types of transplants.

8.1.1.12. Question 12:

Is there a significant difference between the two treatment groups in respect of

a. the proportion of subjects
b. the combination of drugs taken by individuals
c. the duration of intake

as immunosuppression definitely increases the risk for IFI?

8.1.1.12.1. Pfizer response

There was no significant difference in the proportion of patients who received at least one immunosuppressive agent while receiving study drug prophylaxis: 98.2% (220/224) for voriconazole, 97.9% (236/241) for itraconazole. We did not compare the proportion who received combinations of these agents. The median duration of use was 87.08 days for voriconazole and 70.08 days for itraconazole. Concomitant medications were only captured during the time that patients were receiving study drug, and the duration of study drug was longer for voriconazole patients.

8.1.1.13. Question 13:

Would the administration of voriconazole for a longer period or as primary prophylaxis in a later stage following HSCT result in major differences to the described outcomes? The median time of diagnosis of breakthrough IFI in patients receiving voriconazole has been cited as 180 days after STC (Imhof et al.; Clinical Infectious Diseases 2004; 39:743–6);

Fukuda et al.(Blood, 2003 102: 827-833) reported 107 days as median duration for the occurrence of mould infections after STC. To reframe the question: what would be the maximum duration of recommended use of voriconazole for prophylaxis of IFI or is this up to the physicians' discretion?

8.1.1.13.1. Pfizer response

We believe that the study results support the use of voriconazole as primary prophylaxis for at least the first 100 days after allo HSCT and for up to an additional 80 days if immunosuppression persists.

8.1.1.14. Question 14:

For which age groups is an extension of indication sought? The youngest participant in Study A1501073 was 11 years of age (being almost 12 according to the report) with age ranging from 11 to 70 years and an average of 43 years.

8.1.1.14.1. Pfizer response

We are seeking an indication for primary prophylaxis in allo HSCT recipients in adults and in adolescents who are at least 12 years old. We are not seeking an indication in the remaining paediatric population.

8.1.1.15. Question 15:

Clinical relevance of plasma levels is not known for many fungal species. However, the range of voriconazole plasma concentrations measured at day 14 seems rather wide, ranging from <10 ng/ml to10,000 ng/ml – is this of clinical relevance in respect of IFI prevention in HSCT patients? Would plasma level monitoring be necessary?

8.1.1.15.1. Pfizer response

The samples were collected at random times after drug administration. We identified 34 patients (15.2%) with trough levels measured; the median concentration was 0.85 µg/mL (range: 0 - 4.53 µg/mL), and concentrations were > 0.5 and > 1 µg/mL L in 22 (64.7%) and 13 (38.2%) of these patients, respectively. the trough concentration range was not different from that observed in healthy subjects receiving the same dosing regimen. For example, in the pharmacokinetic study A1501092, 34 healthy subjects received the 200 mg PO BID regimen and the results showed that the median trough concentration in these subjects was 0.46 µg/mL, with a range of 0.14 – 4.27 µg/mL.

Considering that there were relatively few cases of breakthrough IFI in the voriconazole group (3 subjects), it is deemed that the exposure associated with 200 mg PO BID dose would be adequate to prevent IFI's, with no requirement for routine plasma level monitoring.

8.1.1.16. Question 16:

Taking prophylaxis beyond day 100 has apparently only positive effects on the defined efficacy outcomes. Subjects don't count as failure anymore after day 100 but prophylaxis might (if study medication is not detrimental to life) have a beneficial impact on survival and IFI. On the other hand, longer administration of prophylaxis might point to the presence of certain indications (as outlined in the study protocol and better AE profile). What is the proportion of subjects in each group taking prophylaxis for 100- 180 days?

8.1.1.16.1. Pfizer response

The proportion of patients continuing study drug prophylaxis for more than 100 days was 96/224 (42.9%) for voriconazole and 68/241 (28.2%) for itraconazole. In the itraconazole group, 34/241 (14.1%) patients received voriconazole and 11/241 (4.6%) patients received posaconazole prior to day 180 which may have prevented the development of IFI's on the itraconazole arm of the study.

8.1.1.17. Question 17:

Another risk factor that is repeatedly linked with risk for IFI after HSCT (for instance by Fukuda et al.) is cytomegalovirus. Has this risk factor been assessed or what is the rationale for not doing so (of minor concern because of the small numbers of IFI)?

8.1.1.17.1. Pfizer response

Cytomegalovirus infection was reported as an adverse event in 31/234 (13.2%) patients who received voriconazole and 26/255 (10.2%) patients who received itraconazole. Based on the adjudication of the second DRC, 2 patients with CMV infection developed probable/possible IFI in the study; both had received itraconazole prophylaxis.

8.1.1.18. Question 18:

Categories as stated in the proposed PI for the number of patients taking voriconazole for more than 12 weeks and 6 months differ from those reported in Module 5 which prevents verification of these figures. It appears as thirty-one patients (28 without site 1028) took prophylaxis for more than 181 days (6 months) in study A1501073; which would result in a bigger sum than the reported one?

8.1.1.18.1. Pfizer response

In the A1501073 study (MITT without site 1028), 123 subjects received voriconazole for > 84 days and 28 subjects received voriconazole for >180 days. In the A1501038 study, 23 subjects received voriconazole for > 84 days whereas none received it for > 180 days. The categories as stated in the proposed PI for the number of patients taking voriconazole for more than 12 weeks and 6 months has been amended accordingly.

8.1.1.19. Question 19:

How important is the lack of efficacy of voriconazole against mucormycosis given that breakthrough mucormycosis "in patients with haematological diseases or HSCT recipients receiving voriconazole for prophylaxis against fungal infection, empirical therapy of febrile neutropenia, or both" occurs in up to 9% of post HSCT IFI (Hsin-Yuns Sun, Singh; The Lancet Infectious Dieases, Vol 11, Issue 4, April 2011, p 301-311).

8.1.1.19.1. Pfizer response

Physicians need to be aware that breakthrough mucormycosis can develop in allo HSCT patients, and that this infection should be one of the considerations in a patient who develops fever and sino-pulmonary infection while receiving voriconazole prophylaxis.

8.1.2. Study A1501038

8.1.2.1. Question 1:

Information about demographics and baseline characteristics of subjects is rather scarce (no information about conditioning regimen, ethnicity, CMV, etc.). The population participating in the trial might be quite heterogeneous and failure/success of prophylaxis might happen disproportionally often in particular groups of HSCT recipients?

8.1.2.1.1. Pfizer response

Additional information regarding the baseline characteristics of patients was included in the publication (Cordonnier *et al*, 2010). The primary diagnosis was acute myelocytic leukaemia in 31 patients, acute lymphocytic leukaemia in 7, unspecified acute leukaemia in 1, and mycosis fungoides in 1. The conditioning regimen was myeloablative in 27 patients (60%), including 14 patients who received total body irradiation, and non-myeloablative in 18 (40%), including seven given total body irradiation. The most common source of stem cells for HSCT was the peripheral blood (n=38; 84%), followed by bone marrow (n=6; 13%) and cord blood (n=1; 2%). Twenty-four patients (53%) were transplanted from a family donor, including HLA-identical

siblings (18 patients), HLA mismatched relatives (5 patients) and an identical twin (1 patient); 21 patients (47%) were transplanted from an unrelated donor.

8.1.2.2. Question 2:

The case definition of probable cases in study A1501038 is a modification of the EORTC criteria of probable fungal infection. It allows the inclusion of cases with a halo sign in CT without any microbiological evidence which is in contrast an integral part of the diagnosis as suggested by EORTC. A reference is made to the papers by Herbrecht et al. (N Engl J Med. 2002; 347(6):408-15.) and Cornely et al. (Clin Infect Dis. 2007; 44 (10):1289-97) who applied the same case definition previously. The first writes, however, that "The largest discrepancy between the diagnoses of investigators and the determinations of the data-review committee resulted not from misinterpretation of the diagnostic criteria but from the lack of confirmation by the radiologists on the data-review committee of the presence of a halo or air-crescent sign on a CT scan of the lungs in 60 cases." And the second refers to an expert panel that suggested this approach (De Pauw and Patterson; Clinical Infectious Diseases 2005; 41:S377–80). This expert panel further highlights that "However, it is important that patients with mycological evidence of fungal disease remain the backbone of the populations intended for epidemiological surveys and trials of therapy". And indeed, in 2008 the diagnostic criteria for invasive fungal disease were modified (De Pauw et al.; Clinical Infectious Diseases 2008; 46:1813–21), yet the requirement of microbiological evidence for the category "probable" has not been dropped; quite in contrast "Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD". In light of this development (which happened after conducting study A1501038) how likely is the misclassification of possible cases as probable IFI?

8.1.2.2.1. Pfizer response

There were 31 patients with previous aspergillosis, of whom 6 were categorized as proven and 25 were categorized as probable, using the 2002 EORTC criteria. Had the unmodified EORTC-MSG definitions for probable invasive fungal infection been applied, five patients in the group with probable infections would have been classified as possible cases. There were no breakthrough aspergillosis infections reported in this study.

8.1.2.3. Question 3:

The change in the EORTC/MSG criteria in 2002 led to a study amendment (No 3).Where in the submitted dossier are the respective changes listed?

8.1.2.3.1. Pfizer response

Amendment No. 3 included a change in the definition of IFI based on the recently published European Organization for Research and Treatment of Cancer / Mycoses Study Group (EORTC/MSG) criteria (Ascioglu et al, 2002). The definition of IFI was modified to accept a halo sign on imaging, plus appropriate host and clinical criteria.

8.1.2.4. Question 4:

Why does the proposed PI contain results from the MITT population which features more favourable outcomes in respect of IFI (7.5%) than the complete case analysis (10.3%); especially considering that the complete case analysis is the more conservative approach? Also data in respect of survival stems from an analysis based on the MITT population which raises the same question.

8.1.2.4.1. Pfizer Response

A "complete" case was defined as a patient in whom the outcome (breakthrough IFI) was observed and/or the subject was evaluable for the entire study period. There were 14 subjects in the MITT that were not evaluable for the entire study period: 11 subjects died, 1 subject was

lost to follow-up, 1 subject withdrew and 1 withdrew due to an adverse event. In 2 of these cases, the outcome was observed (breakthrough IFI) so they were included in the complete case analysis. The remaining patients were not considered complete cases because they died and as a result were technically not evaluable for the entire study period. However, these patients did not develop a breakthrough IFI before they died, and should be included in the primary analysis.

8.1.2.4.2. Evaluator comment

It is accepted that according to the Statistical Analysis Plan, the primary analysis was based on the modified intent-to-treat population with a supporting analysis based on the per protocol population and that the result of the primary analysis is appropriate for inclusion in the Product Information.

8.1.2.5. Question 5:

Please provide further information in respect of concomitantly administered empirical antifungal therapy. According to the list of concomitant medications, for instance 12 out of 45 subjects received amphotericin, 7 subjects received fluconazole, etc. How has a successful secondary prophylaxis been differentiated from the influence of concomitant empirical antifungal treatment? How long (how many days) did subjects receive empirical therapy and what was the proportion overall?

8.1.2.5.1. Pfizer Response

Allo HSCT patients receiving prophylaxis can develop fever unresponsive to antibiotics that could potentially be caused by an IFI. The protocol specified that in patients with fever unresponsive to antibiotics, systemic empiric antifungal therapy must be initiated, pending the results of a diagnostic procedure. If an IFI was ultimately confirmed, the patient would be considered to be a failure in the study. Otherwise, the use of several days of empirical antifungal treatment without confirmation of an IFI was not considered to be a failure.

There were 3 patients who received non-study antifungal agents for an identified breakthrough IFI (**[Information redacted]**). The 6 remaining patients received an antifungal agent for another reason; in none of these was a breakthrough IFI confirmed. The details of these cases are as follows:

[Information redacted] received ambisome for 23 days for pneumonia

[Information redacted] received voriconazole for 32 days for pericarditis

[Information redacted] received caspofungin for 9 days for presumed infection

[Information redacted] received ambisome for 85 days for “antifungal” (likely prophylaxis)

[Information redacted] received amphotericin B for 11 days for oral candidiasis

[Information redacted] received voriconazole for 13 days for pneumonia

Evaluator response: Use of non-study antifungal agents for between 9 and 85 days may have confounded results

8.1.2.6. Question 6:

Is there an oral loading dose suggested? The proposed PI contains neither a separate dosage advice for secondary prophylaxis nor an oral loading dose regimen for primary prophylaxis.

8.1.2.6.1. Pfizer response

Although an oral loading dose was allowed in study A1501038, we do not plan to recommend an oral loading dose for this indication because most allo HSCT patients may have impaired oral absorption at the initiation of prophylaxis. Therefore, we recommend that prophylaxis with voriconazole be initiated with the intravenous loading dose only.

8.2. Safety

8.2.1. Question 1:

It is noted that in study A1501073 the proportion of the event death differed between the two groups in respect of the primary diagnosis. Twenty percent of patients who died in the voriconazole group were diagnosed with acute lymphocytic leukaemia whilst the respective figure was 6.4% in the itraconazole group. Forty percent of patients who died in the voriconazole group were diagnosed with acute myeloid leukaemia versus 51.1% in the itraconazole group. Is this difference attributable to a differential impact of prophylaxis on death-rates according to the underlying diagnosis or is this observation just due to chance?

8.2.1.1. Pfizer response

We compared mortality rates in patients with acute leukaemia prior to allo HSCT: in patients with acute myelogenous leukaemia, 26/102 (25.5%) died in the voriconazole group compared to 43/119 (36.1%) in the itraconazole group. In patients with acute lymphocytic leukaemia prior to allo HSCT, 9/43 (20.9%) died in the voriconazole group compared to 13/44 (29.5%) in the itraconazole group. A review of the causes of death indicated that the majority were caused by progression of leukaemia.

8.2.2. Question 2:

Table 13.7.1.1. (Module 5, clinical study report) suggests that the change of BUN from baseline values was greater in the voriconazole group; approximately 20% of subjects in Study A1501038 with normal baseline renal function experienced abnormal values later during the study. Is this observation due to an impairment of renal function by voriconazole?

8.2.2.1. Pfizer response

The intravenous formulation of voriconazole contains sulfobutylether-beta-cyclodextrin (SBECD), which has the potential to have an effect on renal function, particularly in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), where accumulation of SBECD may occur. The oral formulation of voriconazole does not contain SBECD and does not have this risk. Considering that the majority of voriconazole given in these studies was the oral formulation, it is unlikely that these changes in renal function were caused by voriconazole.

8.2.3. Question 3:

The protocol of study A1501073 defines the recording period for non-serious AEs as "from the time the subject has taken at least one dose of trial treatment through to 14 days after the last dose of study drug" and for serious AEs "from the time the subject has taken at least one dose of trial treatment through to 28 days after the last dose of study drug". However, many tables show figures for a shorter period, namely for the period of 7 days after the last dose taken. Please provide AEs in adherence to the above classification.

8.2.3.1. Pfizer response

The CSR tables for treatment-emergent adverse events that previously included data up to 7 days after last dose of study drug have been regenerated with data up to 14 days after last dose of study drug.

8.2.4. Question 4:

The submitted PSUR for the period March 2010 to February 2011 did not reveal any new safety risk in respect of skin cancer, incl. SCC. However, this risk is of particular interest in Australia given it is the country with the highest incidence of non melanoma skin cancer (NMSC) worldwide (Lomas et al.; Br J Dermatol., 2012 Jan 17). It seems quite likely that

underreporting is present. The study by Vadnerkar, et al. which is part of the risk management plan "suggested that prolonged use of voriconazole is a risk factor for SCC after lung transplantation, particularly among older patients residing in areas with high sun exposure". What is the risk-benefit estimation from this point of view? And with which certainty can an elevated risk for NMSC linked with voriconazole be excluded for Australia; particularly among patients of Caucasian origin (fair skin type). Or, what rate of new NMSC would result from use of voriconazole for the proposed indications in Australia?

8.2.4.1. Pfizer response

We recognize that there have been reports of NMSC in patients who have received voriconazole prophylaxis for relatively long periods of time. However, these reports of NMSC have been predominantly in lung transplant patients, who are recognized to be at risk for NMSC. In contrast, SCC is rare in allo HSCT patients. There were no reports of NMSC in either of the two voriconazole prophylaxis studies in this submission.

Physicians who prescribe voriconazole prophylaxis should be aware that squamous cell carcinoma of the skin and melanoma have been reported in transplant patients during long-term therapy. Patients should avoid intense or prolonged exposure to direct sunlight during voriconazole treatment, and if a patient develops a skin lesion consistent with squamous cell carcinoma or melanoma, voriconazole should be discontinued.

8.2.5. Question 5.

The published article Effects of erythromycin on voriconazole pharmacokinetics and association with CYP2C19 polymorphism comes to the conclusion that CYP2C19 genotypes and CYP3A4 inhibitor erythromycin can influence the plasma concentration of voriconazole, and erythromycin increases plasma concentration of voriconazole in a CYP2C19 genotype-dependent manner. However, the proposed PI states that macrolide antibiotics had no significant effect on voriconazole Cmax and AUC. Please clarify this issue.

8.2.5.1. Pfizer response

The drug interaction study referenced in this article (Shi et al, 2010) tested only a single dose regimen of voriconazole, which does not mirror clinical practice. In contrast, all of our drug interaction studies were designed as multiple-dose studies. Specifically, our drug interaction study with erythromycin evaluated the effect of 7-day regimen (1 gq12h) of erythromycin on the pharmacokinetics of voriconazole (200 mg oral q12h for 10 days) (Purkins *et al*, 2003)[3]. This study demonstrated no clinically significant effect of erythromycin on the pharmacokinetics of voriconazole.

9. Summary and discussion of efficacy

9.1. Study AI501073

9.1.1. Summary of efficacy

Study A1501073 was a multicentre, randomized open label, non-inferiority trial. The primary objective was to compare the success of antifungal prophylaxis with voriconazole versus itraconazole at 180 days post transplant (Visit 9). The primary endpoint was the success of antifungal prophylaxis at Visit 9. To be a success at Visit 9, the subject had to meet all 3 of the following conditions:

[3] Purkins L *et al*. No clinically significant effect of erythromycin or azithromycin on the pharmacokinetics of voriconazole in healthy male volunteers. *Br J Clin Pharmacol* 2003;56 Suppl 1:30 - 36

- Be alive at Visit 9,
- Have no breakthrough proven or probable IFI by Visit 9, and
- Be considered a success at 100 days post-transplant (Visit 7) defined as follows:
  - Be alive at Visit 7
  - Have no break-though proven or probably IFI by Visit 7
  - Meet both of the following conditions:
    - Have no discontinuation of study drug for more than 14 days by Visit 7 for any reason (including empiric therapy, alternative prophylaxis and no prophylaxis)
    - For patients randomised to itraconazole, no more than 14 days of itraconazole capsules could have been taken by Visit 7.

Success in these terms was reported for 48.7% in the VRZ 33.2% in the ITZ group. The comparison between voriconazole versus itraconazole as primary prophylaxis for IFI in HSCT recipients showed non-inferiority and subsequently superiority for VRZ in respect of the primary outcome measure. The difference held when stratifying for conditioning regimen as outlined in the study protocol. The computed odds ratio from a logistic regression model which adjusts the provided prophylaxis for conditioning, relatedness of donor and country computed to 2 in favour of VRZ (95% CI: 1.35, 2.95).

The difference in "success of prophylaxis" at Day 100 was 14.2%. The main driving factor for these observed "success" was the 14.6% difference between the two groups in "insufficient prophylaxis" (not taking prophylaxis for at least 86 days, ITZ capsules for > 14 days, other antifungal treatment for > 14 days).

Differences in observed IFI at Day 180 (3 subjects (1.3%)) in the VRZ group; 4 subjects (1.7%) in the ITZ group), or death (40 subjects (17.9%) in the VRZ group and 44 subjects (18.3%) in the ITZ) did not differ statistically significantly.

Duration until prophylaxis was discontinued varied significantly between the two groups, being 89 days in the VRZ group vs. 72 days in the ITZ group. Most frequently AEs were reported as reason; in a greater proportion of patients discontinuing voriconazole.

Subjects in both groups, almost 40% in the VRZ and 49% in the ITZ group, were treated empirically with other antifungal treatments, ultimately without proven/probable IFI.

The mean duration of hospital stay did not differ significantly between groups. Mean scores for the effectiveness, convenience, and global satisfaction domains from the TSQM were higher at Visit 4 (Day 14) for VRZ compared with ITZ. There were no differences in respect of death at one year or 400 days post HSCT.

9.1.2. Discussion

For patients undergoing haematological stem cell transplantation, fungal prophylaxis is an accepted component of treatment protocols and the decision to use an active comparator is considered justified. Itraconazole is registered in Australia for prophylactic use in such patients. Based on the response to Question 9, its use as comparator for Study AI50103 is accepted.

The two study groups appear to be well randomized with respect to their demographics and baseline characteristics. Statistical requirements for non-inferiority trials as outlined in the EMA guidelines (Note For Guidance On Statistical Principles For Clinical Trials (CPMP/ICH/363/96)) appear to be satisfied; except the non-blinded design.

Breakthrough IFI happened very rarely (1.3% and 1.7%, respectively) in either group. Other authors (Trifilio *et al*. *Bone Marrow Transplantation* (2007) 40, 451–456:18%; see meta-analysis Vardakas *et al*. *Br J Haematol*. 2005 Oct;131(1):22-8: range between studies from 0.3% (Morgenstern *et al*) to 25% (Winston *et al*); Marr *et al*. Clinical Infectious Diseases 2002;

34:909–17: invasive aspergillosis between 4 and 10% in allograft recipients) consistently reported higher numbers.

The need for a composite outcome to reduce study numbers to manageable proportions is considered understandable. With respect to the components of the primary outcome:

- It is biologically plausible that the low infection rate for both groups may be due to prophylaxis. This component of the composite endpoint was potentially subject to confounding due to use of empirical therapy and use of HEPA airflow equipped facilities.
- Survival may be influenced by prevention of invasive fungal infection and thus it is considered an acceptable component of a composite primary endpoint. However, the underlying disease conditions included in Study AI501073 and the transplant treatment would be anticipated to have made a considerable independent contribution to survival or otherwise.
- The third component of the outcome, having no discontinuation greater than 14 days, including for the itraconazole group, no use of capsules for more than 14 days, is considered to have ultimately determined the finding of superiority of voriconazole compared to itraconazole. While probable or proven IFI and need to use substitute treatment would not be subject to bias, other reasons for discontinuation are considered contentious in an unblinded study.
  - Discontinuation due to possible IFI may be influenced by differing interpretation of clinical signs and differing opinions as to the need for, or the duration of interruption of prophylaxis and substitution of alternative treatment.
  - Lack of tolerability of the treatment or unwillingness to continue in the study are considered not to be related to biological plausibility of efficacy and could have reasonably been anticipated a priori to bias against itraconazole solution which is known to be unpalatable. Indeed the applicant's reason for not including a double dummy was the burden of subjecting the voriconazole group to "a placebo containing cyclodextrin which has a recognised tolerability profile".

Although superiority of voriconazole is claimed in the CSR, it is not claimed in the Product Information and based on the above, this is considered appropriate.

Regarding the primary objective, it is recommended that the following definition is included in the Product Information.

The primary endpoint was the success of antifungal prophylaxis at 180 days post-transplant (Visit 9). To be a success at this time point, the participant had to meet all 3 of the following conditions:

- Be alive at Visit 9,
- Have no breakthrough proven or probable IFI by Visit 9
- Be considered a success at 100 days post-transplant (Visit 7) defined as follows:
  - Be alive at Visit 7
  - Have no break-though proven or probably IFI by Visit 7
  - Meet both of the following conditions:
    - Have no discontinuation of study drug for more than 14 days by Visit 7 for any reason (including empiric therapy, alternative prophylaxis and no prophylaxis)
    - For patients randomised to itraconazole, no more than 14 days of itraconazole capsules could have been taken by Visit 7.

The information in the PI includes a p-value indicating a significant difference between the two study drugs in terms of the primary outcome. It is noted that the proposed p-value was not exact i.e. reported as < 0.01. Inclusion of exact figure is recommended.

The proposed Product Information also includes a result for "The proportion of patients who were able to continue voriconazole prophylaxis for 100 days after HSCT... p<0.01)". This is not considered the appropriate outcome for inclusion. The relevant outcome, and that recommended for inclusion in the Product Information is The proportion of subjects with insufficient prophylaxis i.e. those who missed > 14 days of prophylaxis before Visit 7, took less than 86 days of prophylaxis before Visit 7, or, if randomised to itraconazole, took more than 14 days of ITZ capsules before Visit 7. The result was 104 (46.4%) and 147 (61.0%) in the ITZ group, resulting in a treatment difference of -14.6% (95% CI: -23.5%, -5.6%; p=0.0015). This is the outcome which determined the significant difference in the primary outcome analysis and it is important that this is clear to the reader of the Product Information. Thus, although this is a secondary outcome analysis, it is recommended that the exact p-value result is included.

9.2. Study AI501038

9.2.1. Summary of efficacy

Study A1501038 was a non-comparative, open-label, multi-centre study aiming to evaluate the administration of voriconazole for secondary prophylaxis of IFI (patients had either proven or probable IFI in history). The majority of patients were male (62%) with a mean age of 48 years. The majority (84%) received peripheral blood stem cell transplants (47%) of patients had an unrelated donor; 58% experienced GvHD. The most common diagnosis of previous IFI was probable aspergillosis (59%).

The primary finding was recurrent IFI in the MITT population was a total of 3/28 (10.7% [95% CI (2, 28)] patients with proven or probably IFI, compared to 30% of IFI as expected from previous therapies.

9.2.2. Discussion

The sample size was small and the 95% CI stretch from 2% to 28%; the upper boundary being close to 30% which relativises the previous comparison. However, there seems to be no generally recommended regimen for secondary prophylaxis of IFI in HSCT recipients.

In Study AI501038, the major problems related to unblinded study treatment and observational study design, small numbers of participants and the use of non-study antifungal agents by some 40% of patients for between 9 and 85 days may have confounded results.

It is recommended that this primary analysis result is included in the Product Information and that the confidence interval is also included. It is further recommended that the proportion of patients receiving empirical antifungal treatment is included.

10. Summary and discussion of safety

10.1. Study AI501073

10.1.1. Summary of safety

Nearly all subjects in Study A1501073 experienced AEs, more than 99% in both groups. More than half (53% in the VRZ and 55% in the ITZ group) were treatment related. Severe AEs were reported in approximately half of the subjects (53% VRZ and 53% ITZ) but were infrequently attributed to treatment (14% and 12%, respectively). In the sponsor's point of view AEs reported most frequently were associated with leukaemia and its treatment. AEs associated

with hepatobiliary disorders occurred more frequently in the voriconazole group (20.1% versus 11%) as did eye disorders (12% versus 2.7%). There were more serious AEs in the voriconazole group (47% versus 37% all-causality; 8% versus 5% treatment related). Increases in LFT were greater in the voriconazole group.

A high proportion of subjects discontinued study treatment (at least temporarily) in both groups due to AEs- the proportion was higher in the VRZ group (39% all-causality in both groups; 26% versus 22% treatment related).

There was no statistically significant difference in respect of deaths; although it seemed to differ between groups by primary diagnosis (20% of deaths in the voriconazole group had an acute lymphocytic leukaemia versus 6.4% in the itraconazole group whilst the relation was 40% versus 51.1% of deaths with acute myeloid leukaemia as underlying disease).

10.2. Study AI501038

10.2.1. Summary of safety

A total of 26 subjects experienced 59 AEs considered to be treatment related; 9 subjects experienced 45 serious treatment related AEs. Thirteen subjects died but no death was causally attributed to study treatment. Fourteen (14) of 45 subjects (31%) discontinued treatment due to treatment-related AEs. This result confirms the high proportion of subjects who discontinued treatment due to related AE in study A1501073 (~1/4 of subjects).

AEs were similar to those observed in Study A1501073: the most common organ class of treatment related AEs being the hepatobiliary system. Three subjects experienced hallucinations and 3 eye disorders.

Laboratory abnormalities affected mainly haematology and LFT. Apparently approx. 20% of subjects with normal renal function experienced BUN elevations.

10.3. PSUR

No new safety concerns have been identified in this PSUR covering the period from 1st of March 2010 to 28th of February 2011. Worldwide exposure in this period has been estimated with ~207 thousand patients in the USA and ~380 thousand in other countries. Additionally, several studies were newly analysed in this time period which confirmed the known safety profiled. Four studies have been published in this timeframe: one of them did not find evidence of an effect of voriconazole on long-term visual function in patients with paracoccidioidomycosis.

One study reported that both CYP2C19 genotypes and CYP3A4 inhibitor erythromycin can influence the plasma concentration of voriconazole, and erythromycin increases plasma concentration of voriconazole in a CYP2C19 genotype-dependent manner. Pfizer stated that this was a single dose study and that, Pfizer's own study with multiple dosing was not found to influence plasma concentrations to a clinically significant degree. In the absence of details of both studies, it is not possible for the evaluator to make a judgement.

The safety topic hepatobiliary events revealed no new safety concern; however, the University of Wisconsin Hepatic Education Programme which has been introduced in 2009 to raise awareness among physicians for this safety concern seems to have little impact on reporting and will be re-evaluated in the near future.

A search for skin cancer and squamous cell cancer revealed just 16 cases in total. The fact that for instance all 8 cases from the USA were reported by the same physician might be indicative of underreporting.

The reported 32 cases with long term use, defined as more than 90 days, revealed no new safety concern.

11. Benefit-risk assessment

11.1. Assessment of benefit

Invasive fungal infection as complication in recipients of haematopoietic stem cell transplantation is associated with significant morbidity and mortality. *Aspergillus* and *Candida* are the organisms most commonly associated with such infections in this setting and both are generally sensitive to voriconazole. The incidence of probable or proven invasive fungal infection in the two studies including patients with and without prior fungal infection demonstrated low level of probable or proven invasive fungal infection.

Voriconazole in film coated tablet form is likely to be accepted by patients as palatable. Voriconazole in intravenous form allow flexibility in mode of delivery, an important consideration when oral intake is not possible.

11.2. Assessment of risks

Study AI501073 of patients without prior fungal infection did not include sufficient numbers of patients to prove non-inferiority solely in terms of incidence of invasive fungal infection. Study AI501038 examining treatment of patients with prior fungal infection included small numbers of participants and there was no control group. There were possible confounding factors in both studies relating to the decision about use of empirical treatment and there was potential for bias in these unblinded studies.

Prolonged exposure to an antifungal treatment has the potential to result in development of resistance and to result in a shift in the epidemiology of fungal infection. However, this risk is not limited to use of voriconazole.

Cross resistance to azoles may occur among *Candida* species potentially limiting use of other azole antifungal treatments.

Voriconazole has a significant adverse event profile including hepatobiliary disorders, renal disorders, visual disturbances and haematological disorders.

CYP3A4, CYP2C19 and CYP2C9 inhibition or induction results in a considerable potential for drug interactions which may be problematic in a population of patients often requiring multiple medications over the long course of treatment required for prophylaxis.

11.1. Benefit-risk balance

The balance of risks and benefits is considered to lie on the side of benefit.

12. Recommendation regarding authorisation

Extension of the Indication to include prophylaxis of fungal infection is recommended; however, it is recommended that the wording is changed to include the basis for the indication i.e. that the indication is based on studies including patients undergoing haematopoietic stem cell transplantation. The reason for this addition is included in the applicant response to S31 Question 10 regarding transferability of results to other patient populations in Pfizer' words: "We believe that the results of the study apply only to the patient population studied."

It is further recommended that the issues raised with respect to the proposed Product Information and Consumer Medicine Information leaflet[4] are addressed.

[4] Details of these are not included in this CER extract.

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