22 May 2014
EMA/CHMP/379202/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vfend

International non-proprietary name: VORICONAZOLE

Procedure No. EMEA/H/C/000387/II/0097

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 14 June 2013 an application for a variation.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Vfend	VORICONAZOLE	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Vfend SmPC to include information pertaining to the proposed new indication in prophylaxis of invasive fungal infections in high risk hematopoietic stem cell transplant recipients. The Package Leaflet was proposed to be updated accordingly.
In addition, the MAH took the opportunity of this variation to propose an update of the SmPC, Annex II and PL in line with the latest QRD template.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Rapporteur: Hans Hillege

Co-Rappporteur: Pierre Demolis

1.2. Steps taken for the assessment

Submission date:	14 June 2013
Start of procedure:	26 July 2013
Rapporteur's preliminary assessment report circulated on:	24 September 2013
Rapporteur's updated assessment report circulated on:	2 October 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 October 2013
PRAC rapporteur's assessment report endorsed by PRAC on:	10 October 2013
MAH's responses submitted to the CHMP on:	21 February 2013
Scientific Advisory Group (SAG) in Anti-Infectives was held on:	2 April 2014
PRAC rapporteur's assessment report endorsed by PRAC on	10 April 2014
Rapporteur's joint assessment report on the MAH's responses circulated on:	14 April 2014
Rapporteur's updated joint assessment report and readers guidance on the MAH's responses circulated on:	18 April 2014
Second request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2014
MAH's responses to the 2nd RSI submitted to the CHMP on:	30 April 2014

Rapporteur's updated joint assessment report on the MAH's responses circulated on:	13 May 2014
Readers guidance on the MAH's responses circulated on:	19 May 2014
CHMP opinion:	22 May 2014

Information on Paediatric requirements

Pursuant to Article 22 of Regulation (EC) No 1901/2006 as amended, Pfizer Limited submitted to the European Medicines Agency on 22 February 2013 an application for modification of the agreed paediatric investigation plan with a deferral and a waiver as set out in the European Medicines Agency's decision P/42/2010 issued on 31 March 2010, the decision P/198/2010 issued on 27 October 2010, the decision P/74/2011 issued on 5 April 2011 and the decision P/0112/2012 issued on 22 June 2012.

EMA adopted the decision (P/0151/2013) on 05-07-2013 that changes to the agreed paediatric investigation plan (EMEA-000191-PIP01-08-M05), for voriconazole (Vfend), including changes to the waiver, are accepted in line with the opinion (17 May 2013) of the Paediatric Committee of the EMA

The waiver applies to:

- the paediatric population from birth to less than 24 months of age on the grounds that the specific medicinal product is likely to be unsafe
- the paediatric population from 2 years to less than 18 years on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as the needs are already covered.
- for the conditions: treatment of invasive aspergillosis; treatment of candidaemia in non-neutropenic patients; treatment of fluconazole-resistant serious invasive Candida infections (including *C. krusei*); treatment of serious fungal infections caused by *Scedosporium spp.* and *Fusarium spp.*

The Paediatric Investigation Plan (PIP) investigates the targeted indication *Prophylaxis in paediatric (and in adults) patients who are at high risk of developing invasive fungal infections, such as haematopoietic stem cell transplant (HSCT) recipients.*

The agreed paediatric investigation plan entails:

- Open-label, multiple intravenous dose, multi-centre study to investigate the pharmacokinetics, safety and tolerability of voriconazole in children aged 2 to less than 12 years who required treatment for the prevention of systemic fungal infection (A1501007)
- Open-label, multi-centre study to investigate the pharmacokinetics, safety and tolerability of increasing intravenous doses and following a switch to oral voriconazole in immunocompromised subjects aged 2 to < 12 years who required treatment for the prevention of systemic fungal infection (A1501037)
- 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 (A1501081)
- Open-label, intravenous to oral switch, multiple dose study 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 (A1501088)
- a population Pharmacokinetic Analysis of Voriconazole in Children, Adolescents and Adults based on the results of the 4 above mentioned studies A1501037, A1501007, A1501081, and A1501088

- an extrapolation of the efficacy and safety data from the adults studies A1501038 and A1501073, to the subset of patients 24 months to less than 18 years of age.

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0151/2013 on the agreement of a paediatric investigation plan (PIP).

The PIP P/0151/2013 was completed.

The PDCO issued an opinion on compliance for the PIP P/0151/2013.

2. Scientific discussion

2.1. Introduction

Voriconazole (Vfend) is a broad-spectrum, triazole antifungal agent. Its mode of action is inhibition of fungal cytochrome P450 (CYP)-mediated 14α-sterol demethylation, an essential step in ergosterol biosynthesis. Voriconazole is active against a wide range of yeasts and filamentous fungi, including *Candida, Aspergillus, Fusarium*, and *Scedosporium* species. It has proven efficacy in the treatment of both invasive aspergillosis and invasive candidiasis. Voriconazole, which is available in a oral formulation as well as an IV formulation.

Marketing approval has been granted in over 90 countries, including the United States, European Union, and Australia. MA in Europe was obtained in 2002.

In Europe, voriconazole has the following indications:

In adults and children aged 2 years and above in

- *the treatment of invasive aspergillosis;*
- *treatment of candidemia in non-neutropenic patients;*
- *treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei);*
- *treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp.*

The present application is intended to extend the Vfend (voriconazole) indications for a use in prophylaxis as follows:

Prophylaxis of invasive fungal infections in high risk HSCT recipients including:

- *Patients with AML,*
- *Patients who have received myeloablative conditioning regimens*

This application presents the safety and efficacy data from 2 prospective clinical studies and a review of published literature supporting the use of voriconazole for prophylaxis in high-risk patients. The studies are A1501073 (comparative study of voriconazole versus itraconazole as primary prophylaxis in subjects with allogenic HSCT) and A1501038 (non-comparative study using voriconazole as secondary prophylaxis in similar patients).

For this application, the Committee for Medicinal Products for Human Use (CHMP) Guideline on the clinical evaluation of antifungal agents for the treatment and prophylaxis of invasive fungal disease (CHMP/EWP/1343/01 Rev. 1) is applicable.

On 17 May 2005 the MAH requested scientific advice from CHMP (EMEA/CHMP/SAWP/293597/2005) for Vfend concerning the acceptability of the proposed clinical study A1501073 to support the indication for primary prophylaxis of haematopoietic stem cell transplant (HSCT) recipients at risk of fungal infection. The main recommendations of CHMP were:

- The proposed composite primary endpoint is not considered adequate for the assessment of antifungal prophylactic efficacy, as it contains variables not only relating to efficacy but also to safety and tolerability. The CHMP strongly recommends defining a relatively pure primary endpoint consisting of assessment of proven or probable breakthrough infections only. The investigation of overall survival should preferably be included as a key secondary endpoint.

- The use of itraconazole as a comparator in the adult study population is acceptable.

- When conducting the study in an unblinded design it will be essential to follow the provisions to limit possible bias. If compliance and drop-outs are not an issue, blinding might be less important to enable an unbiased assessment. However, if drop-outs will be counted as failures, the opinion of the treating physicians about the efficacy and/or safety and/or tolerability of the investigational drugs can influence the outcome. This is another argument against including the adherence to study drug into the primary endpoint components.

- The Sponsor's study on secondary prophylaxis (A1501038) as well as the primary prophylaxis study conducted by the Blood and Bone Marrow Transplant Group in the USA (the Wingard/Walsh study) may be supportive for the overall benefit/risk assessment of voriconazole, but they cannot serve for demonstration of efficacy for the primary prophylaxis indication targeted in the present development programme.

- In order to enable a meaningful evaluation of efficacy in the prevention of moulds infections e.g. due to *Aspergillus* species, it will be necessary to have an adequate background incidence of infections with those fungi suspected as origin of infections. This should be considered in the selection of participating centres and the recruitment of patients.

- Another crucial element in the evaluation of these studies will be the initiation of antifungal therapy. It would be essential to try to specify the conditions for initiation of empirical antifungal treatment in the protocol as much as possible, with the intention to harmonise these criteria amongst the different participating centres.

In November 2012 the MAH held a pre-submission meeting with the Rapporteur. The intention of the meeting was to discuss MAH's proposals pertaining to the future submission for an indication of prophylaxis for voriconazole in the HSCT population. During this meeting the Rapporteur indicated that their main concern related to patient selection. It was stated that the inclusion criteria were too broad. The Rapporteur recommended that the MAH should clearly define a sub-population from the prospective clinical trials where benefit has clearly been demonstrated in terms of efficacy and the benefit/risk is favourable. However the Rapporteur acknowledged the option to retain the proposed indication if the benefit/risk is justified.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable.

During the assessment procedure, in compliance with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/ SWP/4447/00, June 2006), an updated Environmental Risk Assessment (ERA) has been provided as requested. It concluded that voriconazole does not meet the criteria for classification as a Persistence, Bioaccumulation and Toxicity (PBT) compound. Based on the Phase II Tier A analysis, no environmentally related labels are required for voriconazole. Disposal of unused medicines should follow local guidelines and requirements.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

Following concerns raised by the Hospital Trust for Site 1028, audits of the site by the MAH identifying concerns regarding investigator oversight and conduct, and restrictions on the investigator carrying out clinical research by the General Medical Council in the United Kingdom, subjects from this site were excluded from the analyses of all efficacy endpoints. All subjects were included in the safety analyses. The relevant Ethics Committee and Regulatory Authority were informed. This resulted in 24 subjects (10 in the voriconazole treatment group and 14 in the itraconazole treatment group) being excluded from the efficacy analyses. The MAH confirmed that the SAEs from this site were included in the analyses. Importantly, the exclusion of subjects from the site 1028 did not impact the overall conclusions of the study.

Tabular Overview of clinical studies

Study ID	No. of study centres	Design	Study Objective	Subjects by arm entered/ completed	duration	Primary Endpoint
A1501073	47	Prospective, comparative, open label Phase III	Primary prophylaxis 200 mg bid (after i.v. loading dose)	MITT Voriconazole n=224, itraconazole n =241	Min. 100 days (max. 180 days)	Composite endpoint: breakthrough IFI and survival for 180 days without discontinuation > 14 days
A1501038	17	Non-comparative open label Phase III	Secundary prophylaxis 200 mg bid	N = 40	Min. 100 days (max. 150 days)	Breakthrough IFI

2.3.2. Pharmacokinetic/Pharmacodynamics Modelling

Previously, a pharmacokinetic-pharmacodynamic analysis of patient data from 6 clinical trials (N = 280) could not detect a positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy. However, pharmacokinetic-pharmacodynamic analyses of the data from 10 clinical trials (N = 1121) identified positive associations between plasma voriconazole concentrations and rate of both liver function test abnormalities and visual disturbances. It suggested that subjects with higher voriconazole exposure may have an increased risk of hepatic adverse events or visual disturbances.

Population pharmacokinetic analysis have been obtained using data from study A1501073, i.e. in subjects with allogeneic hematopoietic stem cell transplants (HSCT) receiving primary prophylaxis treatment for invasive fungal infections (IFI)

No population pharmacokinetic analysis using NONMEM was carried out. This can be questioned, as models have already been obtained previously with a lot of data. It is acknowledged that variability may be a problem for the current data set, however this could have been taken into account in making conclusions from the analysis.

The observed range in voriconazole concentrations is rather large, but expected, as concentrations represent those obtained over the whole day, including trough and maximum values.

Trough concentrations ranged from 0 - 4.53 µg/ml (n=34). One subject had a concentration below the limit of quantitation (10 ng/ml), 22 subjects had a trough concentration ≥ 0.5 µg/ml and 13 subjects ≥ 1 µg/ml. Overall, 8 subjects had a plasma concentration below the limit of quantitation.

The observed concentrations were in line with those observed in study A1501092, in which 34 healthy volunteers received oral voriconazole 200 mg b.i.d. In these subjects a median trough concentration was observed of 0.46 µg/ml (range 0.14 – 4.27 µg/ml) and a Cmax of 2.45 µg/ml (range 1.23 – 6.84 µg/ml). Also the voriconazole plasma concentrations observed in adolescents (11 -17 years) were in line with previous obtained data. It is expected that the pharmacokinetics observed during prophylaxis is comparable to that documented for treatment for invasive fungal infections, as the same dose recommendation is applied and in addition, the study population can be considered comparable.

3 subjects (see below) had a breakthrough of IFI:

- subject 10151001, male, 44 years, dose 200 mg oral: pre-dose concentration 1120 ng/ml
- subject 10311001, male, 20 years, dose 200 mg oral: 11.5 h concentration 35 ng/ml
- subject 10431008, male, 64 years, dose 200 mg oral: 3.25 h concentration 2630 ng/ml

The observed concentrations for subject 10311001 can be considered low, but for the other two subjects the pre-dose and the concentration around Cmax are not raising a concern. These limited data do not directly indicate a concern with regard to exposure and breakthrough of IFI.

2.4. Clinical Efficacy aspects

Dose response study

No dose response study was conducted. The MAH proposes to use the therapeutic dose in a prophylactic regimen. This is considered acceptable. Retrospective evidence demonstrates that lower serum concentrations of voriconazole in the current dosing schedule are associated to higher levels of therapeutic failure, it can be accepted that the therapeutic dose was chosen also for use as a prophylactic agent and that a lower dose, which could have resulted in low or lack of preventive activity, was not proposed.

Main Study

Study A1501073 - A prospective, open-label, comparative, multicentre study of voriconazole compared with itraconazole (Sporanox®) for the primary prophylaxis of IFI in subjects > 12 years of age requiring allogeneic hematopoietic stem cell transplant (HSCT). Subjects received study drug immediately following HSCT and continued for a minimum of 100 days to a maximum of 180 days. All subjects were followed for breakthrough IFI and survival for 180 days irrespective of prior discontinuation for any reason.

The following tables summarises the efficacy results from the main study:

Table. Summary of Efficacy for trial A1501073

Title: Prospective, Open-label, Comparative, Multicenter Study of Voriconazole Compared to Itraconazole for the Primary Prophylaxis of Invasive Fungal Infections (IFI) in Subjects with Allogeneic Hematopoietic Stem Cell Transplants (HSCT)		
Study identifier	A1501073	
Design	Prospective open-label randomised active controlled non-inferiority study	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	180 days 7 days <time> <not applicable>
Hypothesis	Non-inferiority	

Treatment groups	voriconazole		IV therapy with voriconazole for 2 days before switching to oral therapy on Day 2. The prophylactic regimen began on the day of initiation of HSCT (Day 0), at least 48 hours after completion of conditioning chemotherapy. For all subjects, voriconazole was administered for a minimum of 100 days to a maximum of 180 days. All subjects were followed for 180 days, irrespective of prior discontinuation for any reason. Study drug prophylaxis could have been continued beyond Day 100, until cessation of immunosuppression or Graft versus Host Disease (GvHD) up to 180 days after transplantation.
	itraconazole		IV therapy with itraconazole for 2 days before switching to oral therapy on Day 2. The prophylactic regimen began on the day of initiation of HSCT (Day 0), at least 48 hours after completion of conditioning chemotherapy. For all subjects, itraconazole was administered for a minimum of 100 days to a maximum of 180 days. All subjects were followed for 180 days, irrespective of prior discontinuation for any reason. Study drug prophylaxis could have been continued beyond Day 100, until cessation of immunosuppression or Graft versus Host Disease (GvHD) up to 180 days after transplantation. Oral solution (200 mg, orally, twice daily [BID], 1 hour before food) was the primary formulation. Subjects were permitted to take itraconazole capsules (dosed at 200 mg BID, immediately after food) for short courses (less than 5 days suggested) where subjects were unable or unwilling to continue on the oral solution.
Endpoints and definitions	Primary endpoint		Success of antifungal prophylaxis at Visit 9 (D180). To be a success at Visit 9, the subject must meet all three of the following conditions: - be alive at Visit 9, - have no breakthrough proven or probable invasive fungal infection by Visit 9, - be a success at 100 days post transplant (Visit 7).
	Secondary endpoints	<label>	- Success as defined above, at 100 days posttransplant - Time to breakthrough IFI - Rates of occurrence of breakthrough IFI - Survival to 180 days posttransplant - Time to discontinuation of study treatment - Survival 1 year after transplant (to be reported separately)

	Additional efficacy endpoints:	<label>	- 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 - Subject-assessed tolerability of therapy - Use of healthcare resources
Database lock	<date>		

Results and analysis

Analysis description	**Primary analysis**				
Analysis population and time point description	Modified Intent to treat at D180				
Descriptive statistics and estimate variability	Treatment group	Voriconazole	Itraconazole		
	Number of subjects	224	241		
	Number (%) of Responders (success at D180)	109 (48.7%)	80 (33.2%)		
	Crude incidence of IFIs	3 (1.3%)	5 (2.1%)		
	death rates	40 (17.9%)	44 (18.3%)		
Effect estimate per comparison	Primary endpoint	Comparison groups		Voriconazole - Itraconazole	
		Number (%) of responders		15.5%	
		95% CI		6.6% - 24.3%	
		P-value		<P-value>	
Notes	The primary endpoint is not appropriate to assess efficacy as discontinuations, which are included in the definition of success, are thought to be largely driven by tolerability and not efficacy. The MAH performed post hoc non-inferiority analyses in two subgroups (patients with AML and patients with myeloablative conditioning) on the incidence of IFI				
Analysis description	**Post hoc non-inferiority analysis:**				
	AML subjects		Voriconazole	Itraconazole	Difference
		IFI rate	1 (1.0%)	2 (1.8%)	-0.8%
		95% CI			-4.0%, 2.4%
		P-value			
	myeloablative conditioning	Comparison groups			
		IFI rate	2 (1.6%)	3 (2.1%)	-0.8%
		95% CI			-3.7%, 2.7%
		P-value			

2.4.1. Methods

Study participants

Patients aged over 12 years requiring allogeneic HSCT were included. Patients with 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", and patients who received any systemically active antifungal agent within the 7 days prior to study entry were to be excluded.

Patients with AML and allogenic HSCT are most susceptible to develop IFI due to prolonged periods of neutropenia and therefore this patient groups were specifically been targeted in Study A1501073.

Treatments

Subjects were randomised to receive either voriconazole (see table below) or itraconazole (200 mg BID) which was administered for a minimum of 100 days to a maximum of 180 days.

	Intravenous	**Oral**	
		Patients ≥ 40 kg	Patients < 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

*It refers to patients aged 15 years and older

Itraconazole as comparator is considered acceptable, however it is not clear why itraconazole capsules were to be administered, since oral solution is the recommended formulation with better bioavailability. (Please refer to IDSA guidelines 2009 on Aspergillosis: "Absorption from the capsular formulation, which is enhanced by low gastric pH and dietary lipids, may be erratic or negligible in the fasting state, particularly in granulocytopenic patients with cancer and in patients with hypochlorhydria, and its use in seriously ill patients with life-threatening infection is not recommended"). Also it is not clear why 14 days as a maximum was introduced in the itraconazole arm. The only justification provided is that capsules were administered to subjects who were unable or unwilling to continue on the oral solution. To evaluate the potential impact, the MAH should provide data on the number of patients in the itraconazole arm that were on capsules both < 14 days and > 14 days in relation to breakthrough infection and use of additional antifungals, because decreased activity can be anticipated that would result in more frequent use of additional antifungal agents or lower protection rates.

Objectives

The primary objective was to demonstrate non-inferiority of voriconazole over itraconazole regarding the "Success" of antifungal prophylaxis at 180 days post-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. 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%.

Secondary objectives included to determine success of antifungal prophylaxis (as defined above), but at 100 days post-transplant and 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.

Outcomes / endpoints

The primary objective is to compare the success of antifungal prophylaxis with voriconazole versus itraconazole at 180 days post-transplant (Visit 9). Thus, the primary endpoint is the success of antifungal prophylaxis at Visit 9.

To be a success at Visit 9, the subject must meet all three of the following conditions:

- be alive at Visit 9,
- have no breakthrough proven or probable invasive fungal infection by Visit 9,
- be a success at 100 days post-transplant (Visit 7).

Note that to be a success at Visit 7 (which itself is a key secondary endpoint), a subject must meet all three of the following conditions:

- be alive at Visit 7,
- have no breakthrough proven or probable invasive fungal infection by Visit 7,
- meet both of the following conditions regarding the amount of study medication taken in the scheduled 100 days of prophylaxis (ie, by Visit 7):
    - have no discontinuation of study drug for more than 14 days by Visit 7 for any reason (this includes empiric therapy, alternative prophylaxis and no prophylaxis),
    - for subjects randomised to itraconazole, no more than 14 days of itraconazole capsules must be taken by Visit 7.

As already indicated in the CHMP advice from 2005, the composite primary endpoint is not considered adequate for the assessment of antifungal prophylactic efficacy, as it contains variables not only relating to efficacy but also to safety and tolerability. As this endpoint is expected to be mainly driven by tolerability (discontinuations) rather than efficacy, it is deemed unsuitable to determine the efficacy of voriconazole in the indication of prophylaxis in HSCT patients. The CHMP strongly recommended defining a relatively pure primary endpoint consisting of assessment of proven or probable breakthrough infections only.

Relevant endpoints for assessing efficacy have been taken along secondary endpoints, namely “Rates of breakthrough IFI” and survival to 180 days post-transplant. Moreover, survival 1 year after transplant is also a relevant indicator. However, no non-inferiority analyses were planned for these endpoints.

Sample size

Sample size calculations in study A1501073 were based on the primary efficacy parameter of success for 180 days after allogeneic HSCT.

Assuming a true success rate of 50% in the voriconazole treatment group and 45% in the itraconazole treatment group, a sample size of 232 subjects per group has 90% power to demonstrate non-inferiority of voriconazole to itraconazole using a pre-specified non-inferiority margin of -10%.

Randomisation

Subjects were stratified at the time of randomization by the following factors:

- Conditioning regimen: myeloablative or non-myeloablative.
- Relatedness of donor: matched related or mismatched/unrelated.

Randomization was also blocked by centre.

Blinding (masking)

The study was not blinded, which could possibly have introduced bias. Clarifications are needed from the MAH to determine how prone to bias the study was. The MAH should confirm whether randomization of patients was done centrally, but also whether a blinded endpoint assessment has been assured.

Statistical methods

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%. The margin was not justified.

Post hoc analysis in subgroups

During the November 2012 Pre-Submission Meeting, the Rapporteur recommended that a subpopulation from the prospective clinical trials should be defined where benefit can clearly be demonstrated in terms of non-inferiority to break-through infections.

For the post-hoc analysis on subpopulations, the MAH has adopted the same methodology as was used for the MITT analysis for each endpoint presented in the Summary of Clinical Efficacy. For any binary endpoint, all proportions are expressed as percentages and all comparisons of difference in proportions between treatments are presented in terms of voriconazole – itraconazole. Unless specified otherwise, approximate two-sided confidence intervals for the difference in proportions are based on the normal approximation to the binomial distribution.

The endpoint of break-through IFI at Day 180 (Day 100) was assessed by calculating the proportion of IFI cases reported in each treatment arm. Voriconazole would therefore, be declared non-inferior to itraconazole if the upper limit of the 95% CI for the difference in IFI rates (voriconazole – itraconazole) is less than 5%.

The MAH has based their non-inferiority margin of 5% on an estimated minimum benefit of itraconazole over placebo of 8.2%. In both populations (AML and myeloablative regimens) a putative placebo IFI rate was established of respectively 15% and 20%. The placebo rate appeared relatively constant in different studies (~15%-20%) yet there is a high, unexplained, heterogeneity in treatment response amongst the different studies. The variation in treatment response between studies cannot be explained by the variables considered. For example, the IFI rate in the fluconazole varies from 2.8% to 25.4% in studies in allogeneic HSCT patients with myeloablative conditioning regimens. For itraconazole the IFI rate varied between 1.6% and 12.6% in these patients. The difference between treatment and placebo, where present, varies accordingly. Due to this high heterogeneity it is questionable whether pooling as done by the MAH is appropriate to determine the non-inferiority margin.

Results

Participant flow

Table 5. Subject Disposition

	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.

Recruitment

First Subject Visit: 8 March 2006

Last Subject Visit: 10 February 2009

Conduct of the study

The most frequently reported protocol violations were SAEs reported outside of the protocol-specified reporting window (21 subjects) and use of antifungal therapy within 7 days of study start (9 subjects). This information is not in line with the information provided in appendix B12, where it is stated that anti-fungal therapy given in the 7 days prior to study entry has been reported for 74 subjects. After reanalysis

the MAH corrected the figures in appendix B12 and mentions 71 subjects with prior antifungal therapy. Further, in Appendix B12 it is stated that one or more Deviations in study procedures/lab tests were noted in 291 patients.

Baseline data

The mean age was approximately 43 years for both treatment groups, with ages ranging from 11 to 70 years. In total, 20 patients aged between 11 and 18 yrs were included, 9 in the voriconazole arm and 11 in the itraconazole arm.

Table 7. Demographic Characteristics (Safety Population)

Demographic Characteristic	Voriconazole N=234	Itraconazole N=255
Sex (n, %)		
Male	138 (59.0)	155 (60.8)
Female	96 (41.0)	100 (39.2)
Age (years; n, %)		
<18	9 (3.8)	11 (4.3)
18 - 44	106 (45.3)	119 (46.7)
45 - 64	104 (44.4)	115 (45.1)
≥65	15 (6.4)	10 (3.9)
Mean (SD)	43.3 (14.4)	42.7 (14.6)
Range	11-70	13-70
Race (n, %)		
White	217 (92.7)	233 (91.4)
Black	0	2 (0.8)
Asian	2 (0.9)	3 (1.2)
Other	15 (6.4)	17 (6.7)
Weight (kg)		
Mean (SD)	73.9 (16.5)	75.6 (17.3)
Range	32.0-116.0	30.0-138.0
Height (cm)[a]		
Mean (SD)	169.9 (10.2)	170.5 (10.1)
Range	135.0-195.0	142.0-203.0

Source: Table 13.2.1
SD = standard deviation
[a]Height data collected for 233 subjects in the voriconazole group and 254 subjects in the itraconazole group.

The requested extension of indication applies to children > 2yrs, and the MAH proposes to extrapolate the safety and efficacy from adults to the paediatric population. This could be accepted however special vigilance is needed with regards to the safety of long-term use of voriconazole in children.

Primary diagnoses & durations for the included patients are presented in the following table:

Table 8. Primary Diagnoses and Durations (Safety Population)

Primary Diagnosis	Voriconazole N=234	Itraconazole N=255
Acute lymphocytic leukemia (n)	43	44
Mean Duration Since First Diagnosis (years)	2.1	1.9
Range	0.2-18.4	0.3-15.4
Acute myeloid leukemia (n)	102	119
Mean Duration Since First Diagnosis (years)	0.9	0.9
Range	0.2-6.3	0.2-6.1
Myelodysplastic syndrome (n)	35	30
Mean Duration Since First Diagnosis (years)	1.5	1.3
Range	0.3-8.8	0.2-6.0
No therapeutic response (n)	45	47
Mean Duration Since First Diagnosis (years)	3.2	4.1
Range	0.0-13.8	0.1-17.6
Chronic myeloid leukemia transformation (n)	6	13
Mean Duration Since First Diagnosis (years)	1.1	1.5
Range	0.3-3.6	0.2-7.4

Source: Table 13.2.2

Numbers analysed

The MITT population consisted of all randomized subjects who received at least 1 dose of randomized study drug and had undergone allogeneic HSCT and included 465 subjects: 224 in the voriconazole group and 241 in the itraconazole group. In the voriconazole group, 39 subjects (17.4%) were excluded from the PP population. In the itraconazole group, 42 subjects (17.4%) were excluded from the PP population.

Outcomes and estimation

Regarding the primary outcome, the difference in success (responder rates adjusted for the randomization strata) was 16.4% in favor of voriconazole (95% CI 7.7% - 25.1%). As such non-inferiority was inferred as was superiority of voriconazole over itraconazole. Results for the PP population were similar. As this endpoint is likely to be largely driven by discontinuations and thus tolerance, it is not considered a good measure for efficacy. The more relevant measures are rates of IFI and survival as also discussed above.

For the rate of IFI, only the MITT analyses were presented in the clinical study report. 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 voriconazole group and 4 subjects (1.7%) in the itraconazole group. In addition, one subject with a probably IFI was reported for the itraconazole arm, which was not initially captured by the study database. An additional analysis of per protocol population was subbmitted upon request. This analysis confirmed the results of the MITT analysis.

Table 15. Summary of Invasive Fungal Infection Details (Including the EORTC/MSG Worksheets) – MITT Population

Subject Number	Result of IFI Analysis	Treatment Emergent?[a]	Pathogen	Body Site of IFI
Voriconazole				
10051002	Probable	No	*Aspergillus fumigatus*	Lung
10311001	Proven	No	*Candida krusei*	Blood
10431008	Proven	No	*Candida parapsilosis*	Blood
Itraconazole				
10181011	Probable	Yes	*Aspergillus* species	Lung
10311002	Proven	No	*Aspergillus fumigatus*	Lung
10321026	Probable	Yes	*Aspergillus* species	Lung
10401003	Probable	No	*Aspergillus* species	Lung
10561001	Probable	No	*Aspergillus fumigatus*	Lung

Source: Appendix A14.2
IFI = invasive fungal infection; EORTC/MSG = European Organisation for Research and Treatment of Cancer/Mycoses Study Group; MITT = Modified Intent-to-Treat
[a]Treatment-emergent IFIs were defined as those that occurred at any time while the subject was on study drug and for 7 days following discontinuation from treatment.

The incidence of IFI in both treatment arms is low, also in comparison to what is expected from previous studies in this indication. Additional analysis excluded the selection of patients as causative factor for the low rates of IFI, nor a short duration of neutropenia. An additional overview of antifungal treatment showed that prior to start of treatment 65/224 (29.0%) in voriconazole treated subjects and 62/241 (25.7%) in itraconazole treated subjects used antifungal therapy, from whom 34/65 and 37/62 within seven days of enrolment. The use of additional antifungal therapy was significantly higher in the itraconazole group compared to the voriconazole group (41.9% [101/241] vs. 29.9% [67/224], respectively). The majority of additional antifungal therapy was administered during the active treatment (i.e., prophylaxis) period (64.2% [43/67] for voriconazole; 60.4% [61/101] for itraconazole). This additional antifungal therapy may contribute to the final outcome to some extent. However other studies allowed preemptive co-treatment in substantial proportions also. Based on the additional analysis it can be concluded that in this risk population both itraconazole and voriconazole are efficacious antifungal agents in the prevention of IFI.

Overall, 84 subjects (18.1%) died at or before day 180: 40 subjects (17.9%) in the voriconazole group and 44 subjects (18.3%) in the itraconazole group. The survival up to day 180 appears similar in both treatment arms, with no significant difference in the death rate at any time point measured. The point estimate on the difference lies around zero. the 1-year survival rate was higher for subjects treated with voriconazole (74.1%) compared with itraconazole (68.9%). This difference (5.2%) is not statistically significant (95% CI for the difference in crude survival, voriconazole – itraconazole: [-3.0 %, 13.4%]; p-value = 0.2109).

The median number of days from the start of prophylaxis until discontinuation of study treatment was higher for voriconazole (98.0) compared with itraconazole (70.0). Additional analysis showed that the combination of intolerance and AE resulted in discontinuation in 66.1% and 68.7% in the voriconazole and itraconazole arm respectively. The proportion of subjects experiencing intolerance among those subjects was highest in the itraconazole arm: 31.4% vs. 12.1% in the voriconazole arm of the total population. On the contrary, the proportion of subjects experiencing AEs among those subjects was

highest in the voriconazole arm: 54% vs. 37% in the itraconazole arm of the total population. This information is to be included in the SmPC.

With regard to the satisfaction as measured by the TSQM score, this TSQM score was a composite endpoint of perceived Effectiveness, Side Effects and Convenience: most differences were in differently scored Convenience appreciation (78.56 vs. 59.01) and relatively smaller differences in Side Effects Score (92.35 vs. 81.53). This implies that the perception of patients on tolerability of voriconazole was not as favourable. However this conclusion is based on 48/244 (20%) patients post visit 4. Because of these flaws in interpretable numbers used for measurement of satisfaction, any conclusions that these satisfaction score support the conclusion of a lower tolerability of itraconazole in the study cannot be made.

Ancillary analyses

Following discussions with the rapporteur, the MAH conducted post-hoc analyses to demonstrate non-inferiority of voriconazole compared to itraconazole in preventing IFI in two subpopulations considered to be at high risk of IFI: patients with AML and patients with myeloablative conditioning regimens. The MAH judged these two populations to be at high risk of IFI, therefore justifying the use of voriconazole for the prevention of IFI. Analyses in these subgroups largely mirrored the primary analysis for the whole study population, however the primary objective was to establish non-inferiority of voriconazole over itraconazole regarding the incidence rates of IFI.

Of the total 465 subjects in Study A1501073, 44.5% had underlying AML. A total of 3 AML subjects, 1 subject (1.0%) in the voriconazole group and 2 subjects (1.8%) in the itraconazole group, developed a proven or probable IFI during the study period (from the start of prophylaxis until Day 180), and 1 in each group during the first 100 days. At Day 180, this represented a difference of -0.8% (95% CI -4.0%, 2.4%). This difference was not statistically significant, and non-inferiority was demonstrated since the upper limit for the difference is <5%.

There was a slight but not significant difference in crude death rates between voriconazole and itraconazole. For voriconazole at Day 180, there were 16 deaths (crude death rate 16.3%) and for itraconazole there were 22 deaths (crude death rate 20.2%). The difference between the 2 treatments (voriconazole – itraconazole) was -3.9% (95% CI: -14.4%, 6.7%).

A total of 268 subjects with myeloablative conditioning (125 in the voriconazole treatment group and 143 in the itraconazole treatment group) were included in the MITT analysis of Study A1501073. A total of 5 subjects receiving myeloablative conditioning, 2 subjects (1.6%) in the voriconazole group and 3 subjects (2.1%) in the itraconazole group, developed a proven or probable IFI during the study period (from the start of prophylaxis until Day 180). At Day 180, this represented a difference of -0.5% (95% CI -3.7%, 2.7%).

Considering the expected placebo response of 15-20%, we can consider that voriconazole has efficacy in preventing IFI. This is also a rational extrapolation of the established efficacy of voriconazole in the treatment of invasive aspergillosis (Herbrecht, NEJM, 2002).

The MAH has defined these two subpopulations in which they consider the risk of IFI sufficiently large to justify prolonged use of voriconazole without immediate, evident, benefit to the patient. Patients with AML or those who have received myeloablative conditioning regimens were identified as being at high risk for the development of IFI as they are likely to have prolonged periods of neutropenia. However, rates of IFI in these subgroups were similar to the overall study population, and lower than what would be expected in a population at high risk: in the itraconazole arm a rate of 10-15% would be expected. This

questions whether the selected subgroups are indeed at high risk of IFI or whether the use of alternative, additional, antifungal agents could have resulted in low IFI incidences compromising the overall sensitivity of the study to demonstrate efficacy. Possibly frequent administration of additional antifungal therapy was used to obtain the observed very low IFI rates in these subjects.

An additional overview of antifungal treatment showed that prior to start of treatment 65/224 (29.0%) in voriconazole treated subjects and 62/241 (25.7%) in itraconazole treated subjects used antifungal therapy, from whom 34/65 and 37/62 within seven days of enrolment. This additional antifungal therapy may contribute to the low IFI rate to some extent. However other studies allowed preemptive co-treatment in substantial proportions also.

Supportive study

Study A1501038 – a Phase 3, 12-month prospective, non-comparative, open-label, international multicenter study of voriconazole as secondary prophylaxis for IFI in subjects undergoing HSCT

In addition to the pivotal study, the MAH submitted a prospective, open-label, non-comparative, multicentre study for the *secondary prophylaxis* of IFI with voriconazole in subjects ≥ 18 years of age with allogeneic HSCT with previous history of IFI. Subjects meeting inclusion and exclusion criteria started prophylaxis treatment at least 48 hours after the end of chemotherapy and were continued on study drug for a minimum of 100 days post-transplant (to a maximum of 150 days).

Of the 45 patients who received voriconazole prophylaxis in this study, a 10.7% IFI rate was demonstrated using a complete case analysis (3 occurrences among 28 subjects in the MITT population who either developed an IFI by Month 12, or provided an assessment of IFI at the 12-Month Follow Up Visit). The proportion of 10.7% is low, as recurrence of IFI has been reported frequently, up to > 30% of previous IFI. Therefore a clinical benefit can be assumed, unless the selected population was not at risk. However, considering high proportion of patients with AML, almost 70%, and proportion of patients experiencing GVHD, almost 60%, the risk of developing recurrence (or reinfection with IFI) would be substantial, especially in prevention of recurrence of invasive aspergillosis.

The results of study A1501038 are considered supportive to the efficacy of voriconazole in preventing IFI, however due to the lack of a comparative arm and the study considering secondary prophylaxis rather than primary prophylaxis it cannot be considered particularly strong evidence of efficacy in primary prophylaxis.

2.4.2. Discussion on clinical efficacy

A single pivotal randomised active controlled open label phase III study was conducted to support the newly requested indication of prophylaxis of invasive fungal infections in high risk HSCT recipients including patients with AML and patients who have received myeloablative conditioning regimens. In addition, the MAH submitted an uncontrolled open label study in secondary prophylaxis to support the application. Furthermore, two publications of studies evaluating voriconazole in patients with AML were submitted.

The design of Study A1501073, i.e. the selection of a primary endpoint that is not considered adequate for the assessment of antifungal prophylactic efficacy, complicates the assessment of efficacy. The most

relevant parameters are the rates of IFI in both treatment arms as well as the survival at D180 and after 1 year.

The study included a population at high risk of IFI. The duration of neutropenia was provided in only 26% of the patients treated with voriconazole. The mean duration of neutropenia (ANC <500 cells/mm^3) in voriconazole- and itraconazole-treated patients was 31.4 days (range 13-96) and 26.1 days (range 13 to 59), respectively. This is definitely a contributing factor in the increase of risk of invasive fungal disease and constitutes an indication for initiation of prophylaxis.

The rates of IFI in both treatment arms in this study were lower than what has been reported in previous studies. Factors that may explain the reason for low IFI rates are:

- Initiation of prophylaxis at the moment of HSCT and not at the peak of susceptibility during GvHD as was done in some other studies.

- Additionally use of antifungals before inclusion, since this exclusion criterion of not using antifungals in the 7 days before inclusion was not met in 15% of subjects.

- No standardized efforts to establish the diagnosis of fungal disease as the study allowed for a more empiric approach, which may be related to the time of the study: 2006-2009, when the evidence for the use of BAL and galactomannan monitoring was less established.

- Liberal use of antifungals; frequent co-administration of antifungals without proper stopping or starting rules which was evident in >30% of subjects. Voriconazole-use occurred in 14% of subjects allocated to the itraconazole arm, including 13/244 that used both antifungals from the same class concomitantly.

- Due to aforementioned unstandardized diagnostics; IFI's could be potentially missed.

Furthermore, it was clear that the open label study was not optimal in design and execution to determine efficacy and safety of the two compounds.

The survival up to day 180 appears was similar in both treatment arms, with no significant difference in the death rate at any time point measured. The point estimate on the difference lies around zero. the 1-year survival rate was higher for subjects treated with voriconazole (74.1%) compared with itraconazole (68.9%). This difference (5.2%) is not statistically significant (95% CI for the difference in crude survival, voriconazole – itraconazole: [-3.0 %, 13.4%]; p-value = 0.2109).

The MAH conducted post-hoc analyses to demonstrate non-inferiority of voriconazole compared to itraconazole in preventing IFI in two subpopulations considered to be at high risk of IFI: patients with AML and patients with myeloablative conditioning regimens. These post-hoc analyses did not show any difference in incidence of IFI. However here too the rates of IFI were lower than what would be expected. Additional analysis showed that although the placebo rate seems to be relatively constant (~15%-20%) there is a high heterogeneity in treatment response amongst the different studies. The difference between treatment and placebo, where present, varies accordingly. The variation in treatment response between studies cannot be explained by the variables considered. Considering the editorial by de Pauw, NEJM, 2007, much of the heterogeneity of IFI incidence can be explained by center-specific epidemiology of fungal infections, monitoring strategies or pre-emptive treatment strategy. Considering the expected placebo response it can be concluded that voriconazole has efficacy in preventing IFI.

Patient satisfaction analysis was only performed in 48/244 (20%) patients in the voriconazole arm after visit 4, precluding any conclusion on patient discomfort e.g. related to gastrointestinal AEs of either compound.

PK measurements were collected for exploratory reasons and only in 177 from 234 in subjects receiving voriconazole. Dose relations with regards to efficacy and especially safety were already known at the start of the study in the setting of **treatment** of IFI.

The results of study A1501038 are considered supportive to the efficacy of voriconazole in preventing IFI, however due to the lack of a comparative arm and the study considering secondary prophylaxis rather than primary prophylaxis it cannot be considered particularly strong evidence of efficacy in primary prophylaxis.

Additional Expert Consultation (Scientific Advisory Group)

The advice of an Ad-Hoc Expert Group was sought by the CHMP on the following aspects:

1. The experts were asked if the study population in Study A1501073 was representative of at-risk HSCT patient groups requiring antifungal prophylaxis.

During its presentation, the MAH commented that because patients enrolled in Study A1501073 were allogeneic HSCT recipients, and most had documented or presumed neutropenia, they represent a population at high risk for IFI. It asserted that this is consistent with at risk populations recommended for prophylaxis treatment as described in the literature and ECIL 3 guidelines.

The expert group considered that the study population in likelihood included patients with differing grade of risk. However, overall, it was agreed that the patient groups represented enough high risk requiring antifungal prophylaxis but possibly not all individual patients carried the highest risk.

2. The experts were asked if the low incidence of breakthrough IFI could be explained by the selection of study population (low risk population) or the use of additional antifungal treatment (up to 41% of patients)

During the expert group presentation and discussion, the MAH asserted that the low IFI breakthrough rate reported in Study A1501073 is not related to a low risk patient population enrolled in the study.

The MAH commented that the likely reasons for the low IFI rates in this study are:

1. The early initiation (on the day of transplant) of prophylaxis thereby covering both the pre- and post- engraftment periods, and

2. The requirement to use intravenous dosing for at least the first two days of prophylaxis ensuring adequate exposure to the drug early in the risk period.

3. Use of additional antifungals.

The experts were not entirely re-assured with the MAH's explanation stating the reasons for the low incidence of IFI observed. However, in considering the study population, no difference between the groups was noted in mortality and breakthrough fungal infections and no factor could be identified which could significantly impact on study results.

3. The experts were questioned on to what extent they consider that the safety profile of voriconazole with notably the risk of hepatotoxicity and of Squamous Cell Carcinoma is compatible with a prophylactic use.

The MAH recognises the concern regarding the risks of SCC and hepatic toxicity. It re-iterated that most of the hepatic adverse events were classified as either mild to moderate in intensity and none progressed to liver failure. With regards to the risk to develop SCC, it noted that patients reported in the literature are mainly lung/heart transplant recipients who received voriconazole for an extended period

(median: 284 days). Also, it was stressed that the mechanism by which voriconazole may cause SCC is unclear and definitive evidence of causal relationship is lacking. To minimise the risk of hepatotoxicity and SCC, the MAH proposes both routine and additional risk minimisation activities.
The experts considered the arguments and concluded that indeed the risk of hepatotoxicity is manageable and in itself would not preclude the use of voriconazole in the at risk population. Likewise, the risk of SCC is recognised, but taking account of the fact that prophylaxis will be administered for a relatively limited period, again this should not preclude the use of voriconazole. However, attention is drawn that caution should be applied. The pharmacovigilance activities proposed by the MAH were noted.

4. The experts were asked in which specific subgroups of HSCT patients would voriconazole be particularly beneficial in prophylaxis of IFI considering the safety profile.

The experts agreed that there seems to be no specific subgroup best fit to receive primary voriconazole prophylaxis. Further data in that sense would be required for guideline development /recommendation. The group could not identify any specific subgroup which would benefit of prophylaxis, more than any other.

5. The experts were asked if they consider the risk of SCC in immunocompromised patients - that is further increased by phototoxicity associated with use of voriconazole – a limitation for use of voriconazole as antifungal prophylaxis in specific patient groups, e.g. children?

The expert group concurred with the MAH that routine and additional measures introduced by the MAH are expected to minimize the risk of SCC reported with long term use of voriconazole. The proposed revisions of the SmPC clarifying the maximum duration of therapy in prophylactic use (Section 4.2) and further warning prescribers of the need to carefully assess the benefit-risk balance of long term exposure greater than 180 days (Section 4.4) are expected to further instruct prescribers and minimise this risk.

The group considered that, bearing in mind the risks, no further advice can be provided beyond the appropriate warnings and additional risk minimisation measures proposed by the MAH.

6. The experts were asked if voriconazole should be administered for a maximum period of time e.g. 100 days or 180 days.

The MAH commented that based on the evidence generated from prospective randomised trials, the reported risk period for IFI in allogeneic HSCT patients, and the current practice guidance and recommendations, the proposed prophylaxis is for a period up to 100 days. However, certain patients with on-going significant immunosuppression or GvHD may continue prophylaxis for up to 180 days if the benefit-risk evaluation is favourable.

The experts concurred with the MAH's position but it was further expressed that voriconazole prophylaxis should be used for the shortest possible duration, based on assessment of clinical and mycological criteria. It was noted that in the SmPC will recommend the prescriber to use voriconazole for the shortest period needed.

7. The experts were questioned on the possibility to define quantitative TDM targets in order to minimise the risk of Serious Adverse Events of hepatotoxicity, visual disturbances, phototoxicity.

The MAH commented that no formal consensus on the voriconazole exposure-response relationship has been reached due to the complex clinical setting of fungal infections. At this time, no definite guidance could be provided for the interpretation of plasma concentrations of voriconazole in order to minimise the risk of hepatotoxicity, visual disturbances or phototoxicity. Hepatic AEs can be monitored readily through routine laboratory tests. Through clinical evaluation, signs and symptoms of key adverse events can be captured early, thus minimising the risk of SAEs.

The experts accepted that, at present, no data predicting how the use of TDM to reduce risks exist. In the event of hepatotoxicity, the clinician should consider the benefit-risk of further exposure to voriconazole.

The CHMP acknowledged the conclusion of the Scientific Advisory Group and took it into consideration in the discussions to reach the overall conclusion and benefit/risk balance.

2.4.3. Discussion on clinical efficacy in children

In total, 20 patients aged between 11 and 18 yrs were included in Study A1501073; 9 in the voriconazole arm and 11 in the itraconazole arm.

The requested extension of indication applies to children > 2yrs, and the MAH proposes to extrapolate the safety and efficacy from adults to the paediatric population.

With regard to extrapolation of **efficacy** data from the adult studies (A1501038 and A1501073) to the subset of patients 24 months to less than 18 years of age:

- The rationale provided by Applicant is considered comprehensible.
- The conclusion of Applicant that "based on the shared pathophysiology, it is reasonable to expect similar **efficacy** in paediatric patients at voriconazole doses matching the total exposures in adults that demonstrated therapeutic efficacy" is endorsed.
- Extrapolation of the **efficacy** data from the adult studies A1501038 and A1501073, to the subset of patients 24 months to less than 18 years of age, is endorsed.

The currently proposed **dosage adjustments** in section 4.2 of the SmPC seem only relevant for therapeutic use and **not** for prophylaxis. Therefore in the SmPC under 4.2 prophylaxis it is stated that: Dose adjustments in case of lack of efficacy or treatment-related adverse events are not recommended. In case of treatment-related adverse events, discontinuation of voriconazole and use of alternative antifungal agents must be considered (see sections 4.4 and 4.8).

2.4.4. Conclusions on the clinical efficacy

Regardless of the numerous identified and obvious flaws in the submitted study, study A1501073 did include high-risk patients and the low rate of IFI in both arms may be explained by early initiation of antifungal prophylaxis therapy and liberal use of other antifungals. Based on the available information, dose adjustments cannot be advised. Use of voriconazole in secondary prophylaxis is considered acceptable and may be continued until immune status allows discontinuation of prophylaxis. Treatment duration should be limited to periods in which patients are considered at high risk of IFI due to safety concerns (see below). Prolongation of prophylaxis beyond day 180 requires a thorough reassessment of the benefit risk and consideration on the use of other antifungals by the patient and the treating physician.

2.5. Clinical Safety aspects

2.5.1. Introduction

Important safety issues associated with the use of voriconazole as a therapeutic agent are visual disturbances, hepatotoxicity and photosensitivity including a risk of squamous cell carcinoma.

At the time of licensing of voriconazole for **therapeutic use** there were 1214 patients who received voriconazole (therapeutic studies presented in the initial submission). Of these 203 (16.7%) had a duration of voriconazole therapy of greater than 12 weeks, with 56 patients receiving voriconazole for over 6 months. Since licensing it has been found that there could be a direct causal association between voriconazole, photo-ageing and squamous cell cancer. This is of particular concern in children, as the

reporting rate of phototoxicity was found to be higher in children than in adults. Secondly it could limit long term use of voriconazole.

Patient exposure

This submission includes safety data for a total of 534 subjects with HSCT: voriconazole was administered to a total of 279 subjects (234 subjects in Study A1501073 and 45 subjects in Study A1501038); itraconazole was administered to 255 subjects in Study A1501073.

The median duration of exposure during prophylaxis in the submitted study is longer than in therapeutic studies (97 days vs. 54-73 days dependent on the study), however absolute numbers of patients exposed to longer term treatment (>12 weeks) were higher in the therapeutic studies – in which the dose was similar. In total, 120 patients received voriconazole for a minimum of 100 days.

Adverse events

The rate of AEs during the study period were similar, but more frequently SAE were reported in the voriconazole arm.

Frequent treatment-related AEs were in the voriconazole arm visual impairment in 6% and hepatobiliary disorders including cytolytic hepatitis, hepatotoxicity, liver function abnormal (17.1 vs. 6.8%), whereas gastrointestinal treatment-related AEs were more frequent in the itraconazole group (15.8% in voriconazole vs. 41.6% in itraconazole).

Visual disturbances

In Study A1501073, AEs in the Eye Disorders SOC were reported for 56 subjects (23.9%) treated with voriconazole and for 44 subjects (17.3%) treated with itraconazole. Vision related disorders were more frequent in the voriconazole arm: 24 (10.2%) vs 9 (3.5%) subjects.

Hepatotoxicity

Clinically significant liver function test (LFT) abnormalities in overall safety population were observed more frequently for voriconazole than for itraconazole. These events were considered related to treatment in 43 subjects total: 27 subjects (11.5%) in the voriconazole group and 16 subjects (6.3%) in the itraconazole group.

Most of the hepatic adverse events were of mild to moderate intensity and none progressed to liver failure. However, hepatic adverse events resulted in permanent discontinuation of study medication for 50 subjects (21.4%) treated with voriconazole and for 18 subjects (7.1%) treated with itraconazole.

Since the time to return to normal in these cases is missing, clinicians cannot be provided with data from this prophylaxis study in what time frame liver enzymes will return to normal in case of discontinuation. Considering the limited clinical experience in only 3/224 subjects and apparent limited effect on hepatic AEs because in 1/3 hepatotoxicity was not resolved, the SmPC should not contain recommendations on dose reductions in case of AEs when voriconazole is used in prophylactic setting, but should recommend discontinuation and use of other antifungal agents. This has to be included in the SmPC.

In addition, the MAH calculated 30-day occurrence of hepatobiliary disorders and showed in general similar rates in the two arms. Additional analysis showed that the majority of hepatic events (about two thirds) occurred in the first month, but were more frequent in the voriconazole arm. There were a total of 111/234 (47%) subjects in the voriconazole arm and 76/255 (30%) subjects in the itraconazole arm experiencing hepatic events. Of these, 75/111 (68%) subjects in the voriconazole arm and 55/76 (72%) subjects in the itraconazole arm experienced their first hepatic events within 30 days after inclusion. This information should be included in the SmPC.

Phototoxicity and Squamous Cell Carcinoma (SCC)

Photosensitivity has been described in 1% to 2% of patients receiving prolonged treatment with voriconazole. For a full discussion, please refer to the section on post marketing data. Three phototoxicity adverse events were reported for subjects who received voriconazole : two sunburns, and one photosensitivity reaction. There was one report of “lichenoid keratosis” but no reports of skin cancer for voriconazole-treated subjects.

Periostitis

Non-infectious periostitis with elevated fluoride and alkaline phosphatase levels has been reported in transplant patients. No adverse events of periostitis were reported during the study.

QT prolongation

Adverse events of QT prolongation were reported for 4 subjects (1.7%) in the voriconazole group and for 3 subjects (1.2%) in the itraconazole group.

Resistance

Resistance was not determined in the two submitted studies.

Serious adverse event / deaths / other significant events

Study A1501073

The incidence of serious adverse events in the overall safety population (including those that were not treatment emergent) was higher among subjects treated with voriconazole (54.3%) than among those treated with itraconazole (46.3%). Similar findings were reported for subjects with AML and subjects receiving myeloablative conditioning regimens.

A total of 18 subjects had hepatobiliary disorders SAEs during this study: 14 subjects (6.0%) in the voriconazole group and 4 subjects (1.6%) in the itraconazole group. These SAEs were considered related to treatment for 9 subjects (3.8%) in the voriconazole and 2 subjects (0.8%) in the itraconazole group.

Two issues were noted : SAEs related to gastrointestinal intolerability were more frequent in the itraconazole arm and the more frequent treatment-related hepatobiliary disorders were in the voriconazole arm: 9/19 versus 2/14 in the itraconazole arm. The latter was also evident in more frequent serious liver enzyme abnormalities: 6 vs 4, respectively.

The 13 cases in the voriconazole arm that experienced treatment-related hepatotoxicity SAE developed mostly liver enzyme abnormalities in the first 4 weeks (8/13). Ten from 13 recovered although duration

required for normalization is not provided, whereas 2 died. From the total 9 permanently had to discontinue voriconazole, whereas in 4 temporarily medication was stopped.

In conclusion, treatment-related hepatotoxicity is more severe with voriconazole with subsequent discontinuation. Most cases resolved within non-specified time frames. Additional time-AE analysis was submitted. The reported incidence of SAEs and hepatic SAEs over the duration of the study provides insight that most of these SAEs occurred in the first month. It should be taken into account that the number of patients after month 3 decreased rapidly, so the denominator is declining over time. Most likely the most susceptible subjects have been filtered out in the first few months and also potentially toxic co-medication is less frequently subscribed in the period after 100 days.

Death

By Day 180, 40 subjects in the voriconazole group had died (complete cases 18.1%) and 44 subjects in the itraconazole group had died (19.3% complete cases). Death rates at day 100, at day 365 and in the two subgroups were not significantly different between the two arms.

Study A1501038

Serious adverse events were reported in 51.1% of patients and were considered to be related to study drug in 20.0% of patients; the most frequently reported being hepatotoxicity (in 2 subjects).

A total of 12 subjects (26.7%) died before the Month 12 follow-up visit, including 1 subject who died after being withdrawn from the study (lost to follow-up), because of complications of HSCT and/or underlying malignancy.

Study medication was discontinued because of AEs for 21 subjects (46.7%), 12 of these discontinuations were due to hepatic events.

Laboratory findings

A total of 447 subjects had a laboratory value that met a criterion of possible concern (without regard to baseline abnormality): 214 subjects (97%) in the voriconazole group and 233 subjects (99%) in the itraconazole group.

In both treatment groups, the most frequently reported clinical laboratory abnormalities without regard to baseline abnormality were associated with hematology parameters, ie, hemoglobin, hematocrit, platelets, WBC count, and absolute lymphocytes and total neutrophils

Safety in special populations:

Acute myeloid leukaemia

Treatment-emergent SAEs were reported for 49 subjects (48.0%) in the voriconazole group and 51 subjects (42.9%) in the itraconazole group. The incidences of AEs that led to permanent discontinuation of study medication among AML subjects who received voriconazole (34.3%) or itraconazole (37.0%) were similar to rates of discontinuation due to AEs observed for the overall study population (39.3% for voriconazole, and 39.6% for itraconazole). The type of AEs most frequently leading to study drug discontinuation for subjects in the AML subpopulation were hepatobiliary disorders for subjects treated with voriconazole (13.7%) and gastrointestinal disorders for subjects who received itraconazole (10.9%).

Hepatic adverse events were reported for 45 subjects (44.1%) in the voriconazole treatment group and for 41 subjects (34.5%) in the itraconazole treatment group. Hepatic adverse events resulted in permanent discontinuation of study medication for 20 subjects (19.6%) treated with voriconazole and for 8 subjects (6.7%) treated with itraconazole.

Myeloablative conditioning regimen

Treatment-emergent SAEs were reported for 57 subjects (43.8%) in the voriconazole group and 52 subjects (34.9%) in the itraconazole group. The incidences of AEs that led to permanent discontinuation of study medication among MAC subjects who received voriconazole (33.8%) or itraconazole (36.9%) were similar to rates of discontinuation due to AEs observed for the overall study population in the voriconazole treatment group (39.3%) and the itraconazole group (39.6%).

Among subjects in the MAC subpopulation, the incidence of AEs coding to the Hepatobiliary Disorders SOC was higher for subjects treated with voriconazole (28.5%) than among those treated with itraconazole (18.1%). Hepatic adverse events were reported for 63 subjects (48.5%) in the voriconazole treatment group and for 44 subjects (29.5%) in the itraconazole treatment group.

Hepatobiliary AEs resulted in permanent discontinuation of study medication for 25 subjects (19.2%) treated with voriconazole and for 10 subjects (6.7%) treated with itraconazole.

Discontinuation due to adverse events

There were slightly more discontinuations due to treatment related AEs in the voriconazole group compared to the itraconazole group (25.6% vs 21.6%). Among subjects who received voriconazole, the type of adverse events most frequently leading to study drug discontinuation were Hepatobiliary Disorders (15.8%, compared with 4.3% in the itraconazole group).

Gastrointestinal Disorders were the most frequent reason for study drug discontinuation among subjects who received itraconazole (13.7%, compared with 0.9% in the voriconazole group).

Post marketing experience

It is estimated that 5,137,127 patients were exposed to voriconazole worldwide since first approval. It is estimated that in clinical trials, 165,560 children were exposed.

Off-label use in general: According to the data available to the MAH, voriconazole is used in 5% of patients using prophylactic treatment in haematological setting in Europe. This value was stable during the last 4 years (2008 to 2011c). In 2011 voriconazole was used for prophylaxis in 6.9% of haematological patients including HSCT recipients. The MAH stated that given a very restricted number of lung transplant recipients, the prescription databases may not be representative for this population. According to the data among 31,380 recorded patients who received voriconazole in France, Germany, Italy, United Kingdom and Spain in 2010, only 183 (0.6%) were lung transplant recipients. The only country in which the prophylactic prescription was captured in these patients was the UK with 29 subjects. In 2011, of the 32,387 recorded patients who received voriconazole in France, Germany, Italy, United Kingdom and Spain, only 240 (0.7%) were lung transplant recipients but none reported prophylactic use. Given the availability of published reports and case studies from other European countries, the data may not reflect actual voriconazole use in lung transplant recipients.

Similar to the situation described above, there is moderate potential for off-label-paediatric use with voriconazole for the prophylaxis of invasive fungal infections.

The MAH states that no post-authorisation cases of off-label use have identified any safety concerns substantially different from those associated to the use in authorised indications.

Based on the data so far, the current risks as laid down in the RMP describe the safety profile of voriconazole appropriately. The safety profile of children is mostly comparable with that of adults.

However, there are two issues that are of specific concern: long-term treatment and long-term treatment of paediatric patients. So far, 165,560 children have been exposed in clinical trials to voriconazole, it is not suspected that a sufficient number of children has been exposed up to 6 months to be able to extrapolate this for the prophylactic use.

The data so far indicate a higher reporting rate of phototoxicity skin reactions and cases of acute pancreatitis in children. However, as little is known on children, special attention should be given to the use and reactions in children regarding all safety concerns already known.

More skin disorders have been reported in children. The most concerning issue remains the SCC. In Eudravigilance on 03 September 2013, 49 reports of squamous cell carcinoma were included, of which 2 paediatric cases. The exact mechanism of the development of SCC is not yet known. However, phototoxicity may play a role.

Cases of SCC were reported more often with longer durations of therapy with voriconazole. Some cases have occurred within 6 months. In the past, the SmPC has been updated several times to address this risk. There have been reports of SCC when used as prophylaxis as well. There is no reason to assume that the risk of SCC is different with different indications. So far, the most data was known on solid transplant data but cases are occurring in all long-term use.

For the risks of 'Skin cancer' – and for that of hepatotoxicity - educational material including a HCP Checklist, HCP Q&A Brochure, and Patient Alert Card are in place. This educational material has been agreed recently.

Major difficulty is that 'long-term use' has not been clearly defined as yet. In the SmPC warnings are given on use for longer than 6 months, based on the available data at that moment: the most – but not all - SCC cases were seen after > 6 months of duration.

In many SCC cases, voriconazole was used for more than 6 months, extending to years. The MAH applies for an indication for prophylactic use up to 6 months. However, according to the SmPC longer use is possible for the treatment indication. It may be expected that in clinical practice, longer than 6 months use will occur. Furthermore, it is not clearly known whether, apart from SCC, the other safety concerns may occur more frequently as some of them tend to be linked to long-term use as well.

For this reason long-term treatment is not recommended and for voriconazole in general, long term exposure (treatment or prophylaxis) greater than 6 months requires careful assessment of the benefit-risk balance, as is stated in the current SmPC proposal.

Regarding the use in children, reference is made to section 2.6 below (Risk Management Plan) in which the Applicant included more updates and reports on the specific pharmacovigilance on children, with special attention for the long-term use, skin disorders, hepatotoxicity and pancreatitis.

Also, the MAH will be closely monitor the safety data in paediatric patients on prophylaxis treatment through post-marketing surveillance program and take measures if any signal is identified.

2.5.2. Discussion on clinical safety

Gastrointestinal AEs were common in both groups with 10% more subjects in the itraconazole group than in the voriconazole group experiencing these AEs (i.e. at least 40% compared to 30%). This increase resulted in more discontinuations in the itraconazole arm which may be partly related to the open label design.

Regardless of a longer duration of exposure of voriconazole with subsequent more cumulative hepatotoxic events compared to itraconazole, hepatic AEs were more severe and hepatic AEs resulted in permanent discontinuation of study medication more frequently in the voriconazole group: 50 subjects (21.4%) treated with voriconazole and for 18 subjects (7.1%) treated with itraconazole. This increase (at least twice as much) is more than the difference in duration (25%).

Visual disorders were more frequent in the voriconazole arm and are included in the SmPC. Other voriconazole-associated AEs that merit specific consideration due to prolonged administration in prophylactic setting are phototoxicity, risk of Squamous Cell Carcinoma and periostitis, although not observed in the present studies.

Duration of prophylaxis was approximately 30 days longer in voriconazole and more treatment-related AEs were recorded:

- Vision disorders: for voriconazole
- Gastrointestinal: for itraconazole
- Hepatobililiary disorders: for voriconazole, 50% vs. 30% treatment-emergent hepatobiliary disorders including 9 vs. 2 SAEs. However, none of these progressed to liver failure and in case of discontinuation (20% v. 7% in case of treatment-emergent hepatic AEs) these liver enzyme abnormalities were reversible.

In addition, the SAEs were provided. Many single events/disorders were noticed, and although some of these single events were considered treatment related, the clinical condition of patients and concurrent medication may complicate establishing causality. This includes the photopsia in a single case in the voriconazole arm that resulted in permanent discontinuation and resolved subsequently in 3 days.

Two issues merit attention: SAEs related to gastrointestinal intolerability in the itraconazole arm that were more frequent and the more frequent treatment-related hepatobiliary disorders in the voriconazole arm: 9/19, versus 2/14 in the itraconazole arm. The latter was also evident in more frequent serious liver enzyme abnormalities: 6 vs 4, respectively.

The 13 cases in the voriconazole arm that experienced treatment-related hepatotoxicity SAE developed mostly liver enzyme abnormalities in the first 4 weeks (8/13). Ten from 13 recovered although duration required for normalization is not provided, whereas 2 died. From the total 9 permanently had to discontinue voriconazole, whereas in 4 medication was stopped temporarily.

No periostitis was noticed and only 3 cases of phototoxicity without SCC.

2.5.3. Conclusions on clinical safety

Treatment-related hepatotoxicity is more severe with voriconazole with subsequent discontinuation. No liver failure was recorded. Most cases resolved within non-specified time frames.

Considering the non-standardized PK measurements, any relation between AEs or SAEs and plasma exposure of voriconazole could not be determined. As a consequence, dose adjustments in case of AEs during use of voriconazole as a prophylactic agent cannot be advised. Therefore, discontinuation of voriconazole must be considered in case of AEs associated with voriconazole: hepatotoxicity, phototoxicity including SCC, visual disorders and periostitis, and use of alternative antifungal agents should also be considered.

2.6. Risk Management Plan

2.6.1. **PRAC advice**

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 2, the PRAC considers by consensus that the risk management system for voriconazole (Vfend) in the prophylaxis of invasive fungal infections in high risk Hematopoietic Stem Cell Transplant (HSCT) recipients including patients with Acute Myeloid Leukemia (AML) and patients who have received myeloablative conditioning regimens could be acceptable.

With the extension of indication the number of long term paediatric patients using Vfend is likely to increase. Therefore the MAH is asked to discuss and reconsider the feasibility of a PASS in paediatric patients.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Summary of the Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Phototoxicity • Squamous cell carcinoma (SCC) • Hepatic toxicity • QTc prolongation • Visual events • Peripheral neuropathy
Important potential risks	• Skin cancer (non-SCC) • Suicide-related events
Missing information	• Effects in pregnancy • Effects in pediatrics • Off-label use • Resistance

The PRAC agreed

Pharmacovigilance plans

On-going and planned studies in the PhV development plan

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned/Started)	Date for Submission of Final Study Report (Planned or Actual)
Global Antifungal Surveillance Program Category 3	To monitor the in vitro activity of voriconazole against target pathogens and detect the emergence of resistance. This is program includes a subset of isolates surveyed by the comprehensive global antimicrobial resistance monitoring program known as SENTRY.	Resistance	Started: June 2013	Planned: September 2014
PASS (A1501097): Evaluation of the potential association between voriconazole use and squamous cell carcinoma (SCC) of skin among patients with lung or lung/heart transplants. This study is ongoing Category 3	• Primary Objective: To assess the potential association between voriconazole use and the development of SCC of skin in patients with lung or heart/lung transplant. • Secondary Objective: To assess the potential association between voriconazole use and the development of melanoma in patients with lung or heart/lung transplant.	SCC	Started	The final study report is expected in the third quarter of 2015.

Study/Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned/Started)	Date for Submission of Final Study Report (Planned or Actual)
PASS (A1501102) Evaluation of the effectiveness of the additional risk minimisation measures proposed to reduce the risk of phototoxicity, hepatotoxicity and SCC in the EU Category 3	The overall objective of the PASS is to evaluate the effectiveness of the RMMs being implemented in the UK and France to mitigate the risks of phototoxicity, SCC of the skin and hepatic toxicity in patients using voriconazole.	Hepatotoxicity, phototoxicity and SCC	Planned	To be decided

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks		
Phototoxicity	This risk is communicated to HCPs and patients through current labeling: SmPC sections 4.4 Special Warnings and Precautions for Use 4.8 Undesirable effects	Educational/communication materials for HCPs and patients
SCC	This risk is communicated to HCPs and patients through current labeling: SmPC Sections: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects	Educational/communication materials for HCPs and patients
Hepatic toxicity	This risk is communicated to HCPs and patients through current labeling SmPC Sections: 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects 5.2 Pharmacokinetic properties 5.3 Preclinical safety data	Educational/communication materials for HCPs
QTc prolongation	SmPC sections 4.3 Contraindications 4.4 Special Warnings and Precautions for Use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable effects	None proposed
Visual effects (including optic neuritis, papiloedema and other visual concerns.)	SmPC sections 4.4 Special Warnings and Precautions for Use 4.8 Undesirable effects	None proposed
Peripheral neuropathy	SmPC section 4.8 Undesirable effects	None proposed
Important potential risks		
Skin cancer (Non-SCC)	None.	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Suicide-related events	None.	None proposed
Missing Information		
Effects in pregnancy	SmPC section 4.6 Pregnancy and lactation 5.3 Preclinical safety data	None proposed

Effects in paediatrics	SmPC section 4.2 Posology and method of administration/Children and adolescents 4.4 Special warnings and precautions for use 4.8 Undesirable effects 5.1 Pharmacodynamic properties 5.2 Pharmacokinetic properties	None proposed
Off-label use	SmPC section 4.2 Posology and method of administration 4.4 Special warnings and precautions for use	None proposed
Resistance	SmPC section 5.1 Pharmacodynamic properties	None proposed

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice with changes.

These changes concerned the following elements of the Risk Management Plan: the communication plan (Annex 8) of the additional risk minimisation measures for the safety concerns phototoxicity, SCC and hepatotoxicity and the PASS study A1501102 = Evaluation of the effectiveness of the additional risk minimisation measures proposed to reduce the risk of phototoxicity, hepatotoxicity and SCC in the EU planned in a previous variation (II/95).

Taken into account the limitations of the prophylaxis clinical study as discussed above and the recommendations that, when treatment-related AEs (i.e., hepatotoxicity, skin toxicity including SCC, visual disorders and periostitis) appear that voriconazole should be discontinued and alternatives must be considered ; and also considering the key role of the education materials in minimising the voriconazole related safety risks, the CHMP agreed that the previously agreed educational materials should be rolled out throughout the EU as soon as possible.

The pilot phase to be run in United Kingdom and France and the PASS study A1501102 to evaluate the effectiveness of the education material before deployment of the material throughout Europe (as agreed within procedure II-95) were not to be considered opportune anymore.

Consequently, the MAH proposed a new Communication Plan, allowing a prompt dispatch of the educational material throughout Europe. This new Communication Plan (Annex 8 of RMP) was endorsed by the CHMP.

The new information added to the SmPC through this extension of indication, including the paediatric warning in section 4.4 and the information in relating to prophylaxis use, will be added to the educational materials.

In addition, it is noted that the Vfend Annex II, D – 'Conditions and Restrictions with regards to the safe and effectiveness use of the medicinal product' is updated to add the agreed education materials in the 'Additional risk minimisation measures' section .

The MAH also submitted within this extension of indication three reports/updates which were originally requested for the next PSUR (submission 9th of May 2014):

1. Feasibility of a potential active surveillance program using secondary Pharmacoepidemiology Databases or existing population based registries to monitor selected events in patients with long-term voriconazole use
2. Non-interventional PASS (A1501097) Progress Report

3. Feasibility assessment of a potential observational study to evaluate the association between voriconazole use and squamous cell carcinoma (SCC of the skin in children aged less than 18 years: updates on the on-going feasibility assessment.

The detailed assessment of these documents will be performed during the PSUR assessment procedure.

2.7. Changes to the Product Information

During the procedure, the CHMP extensively discussed the proposed PI and some amendments were requested.

It was agreed that the new indication in section 4.1 should be *'Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.*'

The full agreed SmPC and Package Leaflet is found in attachment 1of this assessment report.

The contacts of the local representation for Greece and Cyprus were updated in the Package Leaflet.

Changes were also made to the PI to bring it in line with the current Agency/QRD template.

2.8. Significance of paediatric studies

As per article 45(3) of Regulation (EC) No 1901/2006 and EC's Communication 2008/C 243/09, the CHMP is of the opinion that studies, which are contained in the agreed Paediatric Investigation Plan P/0151/2013, which is completed, and in the case of A1501081, A1501088, a population pharmacokinetic analysis and an extrapolation study have been completed after 26 January 2007, are considered significant.

A1501081 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

A1501088 Open-label, intravenous to oral switch, multiple dose study 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

a population Pharmacokinetic Analysis of Voriconazole in Children, Adolescents and Adults based on the results of the 4 above mentioned studies A1501037, A1501007, A1501081, and A1501088

an extrapolation of the efficacy and safety data from the studies A1501038 and A1501073, to the subset of patients 24 months to less than 18 years of age.

These studies provide meaningful data in the paediatric population.

3. Overall conclusion and impact on the benefit/risk balance

Benefits

The antifungal agent voriconazole was compared with itraconazole for the primary prophylaxis of Invasive Fungal Infections (IFI) in subjects requiring allogeneic hematopoietic stem cell transplant (HSCT) in a prospective, open-label, comparative, multicenter study (Study A1501073). Subjects received study drug immediately following HSCT and continued for a minimum of 100 days to a maximum of 180 days. All subjects were followed for breakthrough IFI and survival for 180 days irrespective of prior discontinuation for any reason. In addition a prospective, non-comparative study (A1501038) was submitted in 43 subjects with allogeneic HSCT with prior IFI to determine efficacy and safety of voriconazole in secondary prophylaxis up to a maximum of 150 days.

Beneficial effects

Voriconazole in the dose of 200 mg bid has proven antifungal activity and is recommended in the treatment of invasive aspergillosis and in other indications.

Voriconazole as a prophylactic agent with the same dose as for treatment demonstrated in the pivotal study similar IFI incidences (respectively 3 (1.3%) vs 5 (2.1%) in the mITT population) compared to itraconazole oral solution, a widely used antifungal prophylactic agent with a B1 recommendation of the ECIL in allogeneic HSCT recipients in the initial neutropenic phase or during Graft versus Host disease. No treatment emergent breakthrough IFI in the voriconazole arm was shown (defined as occurring while receiving study medication or within 7 days of discontinuation).

These clinical benefits determined in all subjects were also evident in two subgroups of patients that most specifically require antifungal prophylaxis due to prolonged neutropenia: patients with AML and patients undergoing myeloablative conditioning regimens.

Patients were able to use voriconazole during a longer period of time (at least 20 days more) compared to itraconazole.

Survival up to day 180 appears to be similar in both treatment arms, with no significant difference in the death rate at any time point measured. The point estimate on the difference lies around zero.

The intravenous formulation of voriconazole allows administration of voriconazole in the lead-in period to rapidly achieve adequate trough levels in patients with vomiting or reduced absorption, such as patients with mucositis or GVHD of the intestines.

Used in secondary prophylaxis 3 out of 28 (10.7%) of patients in the mITT population had a proven or probable IFI at 12 month follow up.

Uncertainty in the knowledge about the beneficial effects

The rates of IFI in both arms in this study are substantially lower than what have been reported in previous studies. Several factors could explain the low IFI rate; e.g. early initiation of prophylaxis (at the moment of HSCT), antifungal use prior to inclusion and a liberal use of antifungals during the trial in line

with the empiric approach adopted in the study, and potential IFI's could have been missed due to a lack of standardized efforts to establish the diagnosis of fungal disease.

The open label design combined with the known gastrointestinal safety profile of itraconazole could have resulted in earlier discontinuation of itraconazole.

Although it is possible to conclude efficacy of voriconazole over placebo, due to the aforementioned reasons it is not possible to draw confirmatory conclusions on the relative efficacy of voriconazole versus itraconazole. Due to lack of IFIs and incomprehensible lack of monitoring of voriconazole trough concentrations in the comparative study, essential information are not available on trough levels required for prophylaxis. As a consequence, retrospective data and preliminary recommendations on trough levels of 0.5 ug/ml cannot be validated.

Risks

Unfavourable effects

Although the occurrence of AEs was similar in both groups, more treatment emergent SAEs were recorded in the voriconazole arm (47% vs. 37%).

More patients in the voriconazole arm experienced hepatobiliary AEs (more than twice as much) than in the itraconazole arm.

An overview of the SAEs showed that SAEs related to gastrointestinal intolerability in the itraconazole arm were more frequent as compared to voriconazole arm. Hepatobiliary disorders were more frequently reported in the voriconazole arm: 9/19, versus 2/14 in the itraconazole arm. The latter was also evident in more frequent serious liver enzyme abnormalities: 6 vs 4, respectively.

The 13 cases in the voriconazole arm that experienced treatment-related hepatotoxicity SAE developed mostly liver enzyme abnormalities in the first 4 weeks (8/13). Ten from 13 recovered although duration required for normalization is not provided, whereas 2 died. In 9 patients voriconazole was permanently, whereas in 4 patients voriconazole was temporarily discontinued.

Furthermore, hepatotoxicity was more severe, as the reason for discontinuation because of hepatobiliary disorders was 12.8 vs. 3.5%, and occurrence of serious hepatobiliary events 6.0% vs. 1.6%, respectively. It may also result in non-justified diagnosis of GVHD of the liver as may be derived from the difference in occurrence of 4.3% vs 1.2%, respectively.

In conclusion, treatment-related hepatotoxicity was more severe with voriconazole with subsequent discontinuation. Most cases resolved within non-specified time frames.

At least 30% of subjects experienced vomiting in the voriconazole group and 40% diarrhoea, which may reduce absorption and adequate serum concentrations and result in requirement of additional antifungals to treat (sub)clinical IFI.

Visual disturbances were more frequent: 23.9% vs 17.3%, including visual impairment in 6.4% vs. 0.8% and visual hallucinations (2.6% vs. 0.8%).

The interaction profile of voriconazole in this group of patients requires continuous caution and additional TDM analyses of co-medication.

In the literature, squamous cell carcinoma is mainly reported in lung/heart transplant patients with prolonged use of voriconazole (median 284 days in Vadnerkar, et al. and 31.2-61.2 months in Feist, et al) which is beyond what is recommended in the voriconazole SmPC for prophylaxis use (Section 4.2). The median duration of treatment of voriconazole in study A1501073 was 97 days in the SmPC a maximum of 100 days is mentioned.

The recommendations for early discontinuation of voriconazole in cases of phototoxicity, premalignant conditions, SCC, when LFTs are markedly elevated, and periostitis, are already approved in the SmPC and would apply to any voriconazole use; including therapeutic and prophylactic use.

Uncertainty in the knowledge about the unfavourable effects

The open label design may have influenced discontinuation rates due unfavourable effects, especially in case of vomiting in the itraconazole arm.

Benefit-risk balance

Importance of favourable and unfavourable effects

IFI is associated with high mortality even with adequate treatment options in place (30% in the voriconazole arm in the Herbrecht study, NEJM, 2002). IFI are reported as major complications after allogeneic HSCT. Prophylaxis with antifungal drugs to prevent IFI in high-risk patients is common and recommended in clinical practice, also considering the lack of reliable diagnostics and the high mortality rate associated with IFIs.

Voriconazole is active against a wide range of yeasts and filamentous fungi, including *Candida* and *Aspergillus*. Voriconazole is available in intravenous and oral formulations and has been proven to be safe and effective for the treatment of IFI's in immunocompromised patients including HSCT recipients. Note that voriconazole is (provisionally) recommended by the European Conference on Infections in Leukemia for prophylaxis in HSCT recipients[1].

Voriconazole is expected to be effective in prophylaxis of IFI in high risk patients receiving allogeneic hematopoietic stem cell transplant recipients. However the risk of serious adverse events including voriconazole-associated hepatotoxicity has to be taken into account when administered.

An additional concerning issue remains the increased risk of SCC. In Eudravigilance on 03 September 2013, 49 reports of squamous cell carcinoma were included, of which 2 paediatric cases. The exact mechanism of the development of SCC is not yet known. However, phototoxicity may play a role. This is not clearly established so the use of extensive sun screen is obligatory, but cannot be seen as a full preventive measure. Cases of SCC were reported more often with longer durations of therapy with voriconazole. Some cases have occurred within 6 months.

[1] Maertens et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3—2009 Update Bone Marrow Transplantation (2011) 46, 709–718; doi:10.1038/bmt.2010.175

Moreover, interaction in the CYP450 pathway complicates administration of co-medication and complicates patient management because it requires additional diagnostic tests or modification of treatment.

Discussion on the benefit-risk balance

Although there was no clear difference in the rate of IFI in patients receiving voriconazole or patients receiving itraconazole, the incidence of breakthrough IFI in the study, including in the itraconazole arm, was considerably lower than would be expected questioning the patient selection and thus the external validity of the study.

However considering the high-risk population included in the study and the putative placebo response in these populations superiority of voriconazole over placebo can be assumed. Treatment-related hepatotoxic SAEs were more frequent in the voriconazole arm (9 vs. 2) resulting in permanent discontinuation and subsequent resolution in most cases. Liver failure was not recorded. Tolerability of voriconazole was better than itraconazole resulting in lower discontinuations due to these AEs and longer duration of prophylaxis.

The increased risk of serious adverse events, including photosensitivity reactions potentially resulting in SCC, associated with the use of voriconazole is a main concern. The recommendations for early discontinuation of voriconazole in cases of phototoxicity, premalignant conditions, SCC, when LFTs are markedly elevated, and periostitis, are already approved in the SmPC and would apply to any voriconazole use; including therapeutic and prophylactic use.

It can be concluded that voriconazole as a prophylactic agent in high risk patients receiving allogeneic stem cell transplantation has a positive-benefit risk balance.

However, in the Product Information, it must be strongly addressed that voriconazole cannot be continued when treatment-related AEs (i.e., hepatotoxicity, skin toxicity including SCC, visual disorders and periostitis) appear, the duration must be restricted, dose adjustments cannot be advised, and alternatives must be considered in case of AEs.

The following extension of indication is considered sufficient as it focuses on the post-allogeneic HSCT period which is the risk period:

"Prophylaxis of invasive fungal infections (IFI) *in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients".*

Furthermore, the CHMP considers that this variation implements changes to the decision granting the marketing authorisation due to a significant public health concern on the following grounds:

Additional conditions or restrictions are considered necessary to be implemented by Member States in order to ensure the safe and effective use of the medicinal product, as discussed in section 2.6 above.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Vfend SmPC to include information pertaining to the proposed new indication in prophylaxis of invasive fungal infections in high risk hematopoietic stem cell transplant recipients. The Package Leaflet is updated accordingly.
In addition, the MAH took the opportunity of this variation to update the SmPC, Annex II and PL in line with the latest QRD template. The contact details of the Greek and Cyprus local representatives were updated in the PL.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Conditions and requirements of the marketing authorisation

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

- Health Care Professional (HCP) Question and Answer Brochure for Phototoxicity, SCC and Hepatic toxicity;
  - Advises HCPs on the risks of phototoxicity, skin SCC and liver toxicity associated with voriconazole use.
  - Provides HCPs with the current recommendations to monitor and manage these risks.
  - Reminds HCPs of use of the HCP Checklist and the Patient Alert Card and how to obtain additional copies.

- Health Care Professional (HCP) Checklist for Phototoxicity, SCC and Hepatic toxicity:
  - Reminds HCPs of the risks of phototoxicity, skin SCC and hepatotoxicity reported with voriconazole use.
  - Provides HCPs with the current recommendations to monitor and manage these risks.
  - Reminds HCPs to discuss with the patient/care giver the risks of phototoxicity/skin SCC and hepatotoxicity, what to look for, how and when to seek immediate attention.
  - Reminds HCPs to provide a Patient Alert Card to the patient.

- Patient Alert Card for Phototoxicity and SCC:
  - Reminds patients of the risk of phototoxicity and skin SCC.
  - Reminds patients when and how to report relevant signs and symptoms of phototoxicity and skin cancer.
  - Reminds patients to take steps to minimize the risk of skin reactions and skin SCC (by avoiding exposure to direct sunlight, use of a sunscreen and protective clothing) and inform HCPs if they experience relevant skin abnormalities.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0151/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (E)C No 1901/2006, significant studies in the agreed paediatric investigation plan P/0151/2013 have been completed after the entry into force of that Regulation.