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SCIENTIFIC DISCUSSION

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1 Introduction

Fungal infections are a major cause of morbidity and mortality in immunocompromised patients. Filamentous mould and yeast-like fungi are ubiquitous organisms found worldwide in many different media. The *Candida* species are the most common cause of fungal infections. However, epidemiologic shifts have begun to occur, most likely due to the prophylactic and empiric use of antifungal agents. Emerging fungal pathogens, such as *Aspergillus*, *Fusarium*, and *Zygomycetes*, are changing the clinical spectrum of fungal diagnoses.

Pathogens

General risk factors for invasive fungal infections are exposure to pathogens, an impaired immune system, and fungal spores. The presence of a colonised environment, partnered with a disruption in a physiologic barrier, potentiates the risk of an invasive fungal infection in an immunologically impaired host, such as a patient infected with HIV, someone taking chronic systemic steroids, or a transplant recipient. In addition, contaminated implanted devices (e.g., catheters, prostheses), external devices (e.g., contact lenses), and community reservoirs (e.g., hand lotion, pepper shakers) have all been implicated as sources of fungal outbreaks.

Candida albicans continues to be the most frequent cause of invasive fungal infections in most patient populations. However, prophylaxis and the widespread use of antifungal agents as empiric therapy for neutropenic fever have led to a shift in the epidemiology of invasive *Candida* infections. Infections with species other than *C. albicans* (*Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida krusei*, and *Candida lusitaniae*) are becoming more prevalent. Due to susceptibility variations between species, species identification and susceptibility testing have become important tools.

The second most common fungal pathogen to cause invasive fungal disease is *Aspergillus*. Found worldwide, *Aspergillus* is able to thrive in almost every environment. The organism is found primarily in soil but is also commonly isolated from water, food, and air. The usual route of infection for invasive aspergillosis is via inhalation of conidia (asexual spores). As a result, the lung is the most common location of invasive infection. The sinuses, central nervous system, and skin are also areas that can become infected. Clinically, the most common species to cause infection are *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus niger*. Despite the availability of antifungal agents to treat infections caused by *Aspergillus*, the morbidity and mortality of invasive aspergillosis remains high.

Antifungal Therapy

Diagnosing invasive fungal infections early, reliably, and definitively continues to be a major challenge to practitioners.

Systemic fungal infections lead to considerable morbidity and mortality in patients with suppressed immune systems, such as HIV, cancer and transplant patients. While the increasing size of such population groups has driven the need for effective treatments and prophylaxis, the advent of HAART and associated declining incidence among HIV patients has limited market growth.

Posaconazole is a triazole antimycotic agent, currently indicated for a range of invasive fungal infections in adults, including invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products. The centralised licence was approved in October 2005.

Up to now fluconazole is the only validated oral therapy in prophylaxis indication. Fluconazole is more reliably absorbed and probably less toxic overall. However, its poor activity on *Aspergillus* is a significant limitation of this therapeutic option.

The proposed new indication for posaconazole assessed in this report is the prophylaxis of invasive fungal infections in high-risk patients.

2 Non Clinical aspects

No new non clinical data have been submitted in support to the request of this extension of indication

3 Clinical aspects

The 2 pivotal efficacy studies submitted are **Study C/ I98-316** and **Study P01899**

Study C/I98-316 (study 316 in this report) was in patients with graft versus host disease following allogeneic stem-cell transplant, treated with high-dose immunosuppressive therapy, and study P01899 (study 1899 in this report) involved patients undergoing chemotherapy for acute leukemia or myelodysplastic syndromes.

Study 316

Design

The study 316 was a multi-centre, randomised, double-blind, double dummy, parallel-group, active comparator-controlled study.

The objective of the study was to evaluate the safety and efficacy of posaconazole oral suspension vs Fluconazole in the Prophylaxis of Invasive Fungal Infections in High-Risk Recipients of Allogeneic Progenitor Cell Transplantation With Graft-Versus-Host Disease (GVHD). The patients included had Grade 2 to 4 acute graft-versus-host disease (GVHD) or extensive chronic GVHD, with intensive immunosuppressive therapy for at least 2 weeks after enrolment.

This study was first designed as a two stages study (first for equivalence then for superiority if equivalence is demonstrated. Further to a specific amendment after the interim analysis of the data obtained the equivalence was changed to a non-inferiority demonstration.

The posaconazole dose was 600 mg daily (200 mg or 5 mL of 40 mg/ml suspension, administered three times daily), taken orally with food. The comparator was fluconazole only, 400 mg daily (100 mg capsules, 4 capsules), taken orally once daily at the same time, preferably in the morning. As a capsule was being compared against a suspension, a double-dummy design was used to enable blinding.

The duration of therapy was 16 weeks, or until an (Invasive Fungal Infection) IFI was suspected or diagnosed.

The use of empiric systemic antifungal therapy was prohibited by the study protocol except for the use of one short ($\leq$5 days) empiric course, and one short ($\leq$5 days) course during a period of study drug interruption (either due to an inability to take oral medication or due to an AE).

Primary Endpoint

Incidence rate of DRC-adjudicated proven or probable[1] IFI within the time period from randomisation to 16 weeks after the start of treatment or 112 days from randomization if study drug was never taken.

The IFI status of the subject was determined by the Data Review Committee (DRC) based on the European Organization for Research and Treatment of Cancer Mycoses study group (EORTC-MSG) criteria.

[1] proven, probable and possible IFI definitions; see: *Clinical Infectious Diseases*, 2002, 34: p7-14

Secondary Endpoint

The clinical outcome was treatment success versus failure where a clinical failure was defined as the presence of a proven or probable IFI or more than 5 consecutive days of empiric treatment with an antifungal other than POS within 16 weeks of start of treatment.

The secondary efficacy parameters were also to be summarized by treatment group (Incidence rate of DRC adjudicated proven, probable, or possible IFI according to the EORTC-MSG criteria, Time to first diagnosis of IFI, Incidence rate of IFI during the follow-up period, Incidence of fungal-related mortality during the study period, All cause mortality during the study period, Performance status (ECOG score) by visit and by treatment group, Grading of GVHD and steroids requirements, Use of empiric systemic antifungal therapy, Incidence of a fungal colonization, Incidence rate of mucocutaneous or superficial fungal infections, Incidence of proven or probable IFI within the time period from randomization to the end of treatment, defined as the time of the last dose of study drug plus 7 days).

Study 1899

Design

The study 1899 was an open label with evaluator blinding multi-centre, randomised, parallel-group, active comparator-controlled study.

The objective of the study was to evaluate the safety and efficacy of posaconazole oral suspension (POS) compared with fluconazole (FLU) or itraconazole (ITZ) in the prevention of invasive fungal infections (IFI) in subjects with prolonged neutropenia due to remission-induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes.

This study was designed to show statistical equivalence (non-inferiority) or superiority between POS and the standard azole (FLU/ITZ) reference arm.

The duration of therapy was until complete remission of neutropenia, or until other protocol-specified endpoints were reached, for up to a maximum of 12 weeks.

All subjects had routine evaluations for the presence of fungal infection at baseline and during the study, this included screening questions, physical examination, Aspergillus antigen testing, and fungal blood cultures/ PCR every 2 weeks, with other investigations as clinically necessary. At any time during the study, if a subject developed a fever, or any other sign or symptom of infection, a complete evaluation was performed.

Primary endpoint

As primary endpoint was defined the incidence of proven or probable IFI from randomization to the end of the Oral Treatment Phase, defined as the period from randomization to last dose of oral study medication plus 7 days (or the discontinuation date for subjects randomized but never treated).
The evaluation of primary efficacy was made in two stages. First, non-inferiority of posaconazole vs. comparator arm was assessed. If non-inferiority was demonstrated, then superiority of posaconazole vs. the comparator arm was assessed.

Secondary endpoints

The clinical outcome was used as secondary endpoint (treatment success versus failure), and the Incidence of proven or probable IFI.

In addition, the secondary efficacy variables were to be summarized by treatment group (Time to first diagnosis of IFI (proven, probable, or possible IFI, as determined by a panel of external expert evaluators), Time to initiation of empiric parenteral antifungal therapy for suspected fungal infections

(time to onset of febrile episodes refractory to antibacterial therapy from onset of neutropenia), Incidence of IFI (proven, probable, or possible IFI, as determined by a panel of external expert evaluators) during the follow-up period (defined as up to 30 days after the discontinuation/completion of study drug therapy or 100 days after randomization, whichever occurred later), Number of subjects receiving empiric SAF therapy for a suspected IFI during the neutropenic episode, Number of subjects with positive fungal surveillance cultures developing subsequent proven or probable IFI during the Treatment Phase, Incidence of superficial (mucocutaneous) fungal infections during study drug therapy)

Results

i. Results of Study 316

Patient population /Demographic notes

Six hundred subjects were randomized, 301 to posaconazole and 299 to fluconazole.

The majority of subjects randomized in this study had at least two or more known risk factors for the subsequent development of IFI.

Of the 600 All Randomized Subjects, nearly all were between the ages of 18 and 65 (range 13 to 72, median age 43.0 posaconazole and 41.0 FLU), about two-thirds were male in both treatment groups, and most were Caucasian (86% posaconazole, 82% FLU). Approximately two-thirds of subjects had acute GVHD (posaconazole: N=202; FLU: N=197) and one-third had chronic GVHD (posaconazole: N=98; FLU=100). The median time from transplant to baseline date was over 60 days in each group, thus a large majority required long-term antifungal prophylaxis after engraftment due to receipt of intensive immunosuppressive treatment for GVHD. All subjects had been treated with antifungal agents prior to baseline and more than half of these in each group had been treated for more than 14 days. The median number of days of prior therapy was similar between the two groups (16 posaconazole, 19 FLU) and the type and proportion of agents received was also similar.

There were 12 subjects under the age of 18, 4 in the posaconazole group and 8 in the fluconazole group.

In study 316, approximately two-thirds of subjects (69% posaconazole, 64% fluconazole) completed the Primary Time Period (defined as randomization day to 111 days after the Baseline date).
No subjects were mis-randomized. In addition to the 600 subjects properly randomized, three additional subjects were randomized but did not sign informed consent and were not treated; therefore, they are not included in the All Randomized Subjects population (see table below).

	N (%) of Subjects[a]	
Data Set Analyzed	POS	FLU
All Randomized Subjects (n=600)	301 (100)	299 (100)
All Treated (n=579)	291 (97)	288 (96)
Modified Intent-to-Treat (n=445)	211 (70)	234 (78)
Efficacy-Evaluable (n=384)	180 (60)	204 (68)

a: Percentage of subjects is based on the All Randomized Subjects population.

The Efficacy-Evaluable population (≈Per Protocol analysis) is the most relevant in the context of the non-inferiority demonstration. However, it only represents around 65% of the overall randomized population

The table below shows the results on the Disposition of Subjects at End of Treatment by Treatment Group: (All Randomized Subjects)

	POS (n=301)	FLU/ITZ (n=299)
Subjects Who Completed Treatment	165 (55)	144 (48)
Subjects Who Discontinued Treatment	136 (45)	155 (52)
Administrative	0	1 (<1)
Adverse Event	100 (33)	98 (33)
Did Not Meet Protocol Eligibility	3 (1)	7 (2)
Non-compliance With Protocol	8 (3)	10 (3)
Subject Did Not Wish to Continue	17 (6)	15 (5)
Treatment Failure	**8 (3)**	**24 (8)**

The main difference between the two treatment arms in the rate of discontinuation of treatment phase is driven by the more important rate of treatment failure in the FLU/ITZ arm (8% versus 3% in the POS arm).

The table below shows the Disposition of Subjects During the Primary Time Period by Treatment Group (All Randomized Subjects)

	POS (n=301)	FLU/ITZ (n=299)
Subjects Who Completed Primary Time Period	207 (69)	192 (64)
Subjects Who Discontinued From the Study During the Primary Time Period	94 (31)	105 (35)
Administrative	1 (<1)	0
Adverse Event	57 (19)	55 (18)
Did Not Meet Protocol Eligibility	3 (1)	5 (2)
Lost To Follow Up	1 (<1)	0
Non-compliance With Protocol	6 (2)	4 (1)
Subject Did Not Wish to Continue	15 (5)	12 (4)
Treatment Failure	**11 (4)**	**29 (10)**
Disposition Unknown	0	2 (1)

Of the 600 subjects in the All Randomized Subjects population, 349 completed follow-up at Week 24 (186 POS, 163 FLU); 62% of the POS subjects and 55% of the FLU subjects completed Follow-up at Week 24.

The Disposition of Subjects at End of Follow-Up (Week 24) by Treatment Group: (All Randomized Subjects) is shown in the Table that follows

	POS (n=301)	FLU/ITZ (n=299)
Subjects Who Completed Primary Time Period	**186 (62)**	**163 (55)**
Subjects Who Discontinued From the Study During the Primary Time Period	**113 (38)**	**133 (44)**
Administrative	0	1 (<1)
Adverse Event	9 (3)	11 (4)
Lost To Follow Up	1 (<1)	3 (1)
Never Entered Follow-up	99 (33)	110 (37)
Subject Did Not Wish to Continue	3 (1)	5 (2)
Treatment Failure	1 (<1)	3 (1)
Disposition Unknown	**2 (1)**	**3 (1)**

Results on the Primary endpoint of study 316

There were 175 potential cases of IFI provided to the DRC for adjudication of which 62 Proven/Probable IFIs occurred during the study overall per DRC while 43 Proven/Probable IFIs occurred during Primary Time period per DRC (Interval of time which begins on the Randomization Date and ends on the Baseline Date + 111 days)

Analysis of the proven/probable IFIs by pathogens

During the Primary Time Period, the distribution of Proven/Probable IFI by Pathogen Group (All Randomized Subjects) is presented below:

Distibution of Proven/Probable IFI by Pathogen Group (All Randomized Subjects)

	No. Subjects With Proven/Probable IFI	
Pathogen or Pathogen Group	POS	FLU
Aspergillus	**7**	**21**
Candida	4	4
Other Fungi	5	2
Pseudallescheria[a]	1	0
Rhizomucor miehei[a]	0	1
Trichosporon beigelii[a]	1	0
Scedosporium prolificans[a]	1	0
Mould[a]	2	1
All	16	27

a: Specific pathogens under the Other Fungi group are not counted again in the 'All' row.

Per protocol, non-inferiority of POS vs FLU was assessed first then superiority of POS vs FLU was assessed. Proven or probable IFI distribution due to all pathogens During the Primary Time Period, according to Mantel-Haenszel analysis adjusted for GVHD classification (Acute vs Chronic) at Baseline for All Randomized Subjects is presented:

Subjects With Proven/Probable IFI During the Primary Time Period[a]

	POS	FLU	Odds Ratio	P-value	95.01% CI	Max Value[b]
All randomized population	N=301 16 (5)	N=299 27 (9)	0.5614	0.0740	0.2959 – **1.0651**	1.1625
Efficacy Evaluable population	N=180 10 (6)	N=204 20(10)	0.5636	0.1225	0.2479- **1.1918**	**1.1637**

a: Per protocol, the primary efficacy analysis was performed on All Randomized Subjects during this time period.

b: Calculated value corresponding to 15% relative difference in incidence of proven/probable IFI with respect to the incidence of fluconazole and the total number of proven/probable IFI observed.

While on Treatment time period is defined as the period from first dose of study drug to seven days after the last dose of study drug. Unlike the Primary Time Period, the While on Treatment time period does not include time when subjects were not treated with study drug due to early discontinuations or delays in treatment after randomization (as shown below).

Distribution of Proven/Probable IFI by Pathogen Group while on treatment (All Treated Subjects)

	No. Subjects With Proven/Probable IFI	
Pathogen or Pathogen Group n=29	Posaconazole n=7	Fluconazole n=22
Aspergillus	**3**	**17**
Candida	**1**	**3**
Other Fungi[a]	**3**	**2**
Pseudallescheria boydii	1	0
Rhizomucor miehei	0	1
Trichosporon beigelii	1	0
Mould	1	1

a: Specific pathogens under the Other Fungi group are not counted again in the 'All' row.
IFI = Invasive Fungal Infection; While on Treatment = Interval of time which begins on the first day of treatment and ends on the last day of treatment + 7 days; All Treated Subjects = all subjects who received at least one dose of study drug.

It is important to note that the timing of IFIs during the While on Treatment period differed between the treatment groups; in the POS group 5 of the 7 IFIs developed in the first 5 weeks of treatment compared with 11 of 22 that occurred in the FLU group during the first 5 weeks of treatment. After the first 5 weeks, only two IFIs developed in the POS group, while 11 IFIs developed in the FLU group. This timing confirms the efficacy of POS as most of the IFIs occur very early in the study when immunosuppression is maximum.

Aspergillus
It should be noted that the most common infecting pathogen for proven or probable IFI was *Aspergillus*, causing 28 of the 43 total IFIs in the study in the Primary Time Period among All Randomized Subjects (7/16 POS and 21/27 FLU) and the Mantel-Haenszel analysis adjusted for GVHD Classification (Acute vs Chronic) at Baseline gave an OR 0.3121, 95.01% CI 0.1306 – 0.7458, P-value 0.0059.

Results on Secondary endpoints of study 316

Clinical outcome is the main secondary endpoint designed to evaluate a potential treatment effect regarding clinical failure.
A clinical failure was defined as the presence of a proven or probable IFI, or more than 5 consecutive days of empiric treatment with an antifungal other than assigned study drug, within 16 weeks of start of treatment. Subjects not followed for the entire 16-week treatment phase were also considered failures. A similar comparison of the upper 95.01% confidence limit of the adjusted odds ratio for the effect of treatment was to be used to make the treatment comparison with respect to the clinical outcome failure rate.
The distribution of Clinical Failure by Treatment Group All randomized subjects Mantel-Haenszel analysis of clinical failure by Treatment Group adjusted for GVHD at Baseline is presented below:

Analysis of Clinical Failure by Treatment Group Adjusted for GVHD at Baseline

		FLU		POS						
Variable	**IFI**	**N**	**%**	**N**	**%**	**Odd Ratio**	**P-value**	**Lower 95.01% CI**	**Upper 95.01% CI**	**Max. value**
Clinical Failure-per protocol	Total	299	100	301	100	.	.	.	.	.
	no	189	63	202	67	0.8528	0.3612	0.6060	1.2001	1.2391
	yes	110	37	99	33	.	.	.	.	.

Incidence rate of DRC adjudicated proven, probable, or **possible** IFI

The difference in incidence of all IFIs between the two treatment groups was statistically significant for the While on Treatment period in All Treated Subjects is represented below:

POS N=291	**FLU** N=288	Odds Ratio	P-value	95.01% CI	Max Value[a]
20 (7)	41 (14)	0.4411	0.0038	0.2507-0.7759	1.1690

a: Calculated value corresponding to 15% relative difference in incidence of proven/probable IFI with respect to the incidence in fluconazole group and total number of proven/probable IFI during the Primary Time Period.

Incidence rate of IFI during the follow-up period.

This section focuses on both follow-up to the Post Primary Time Period, which is the same as the Post Treatment Phase, (interval of time which begins on the Baseline Date + 112 days and ends on the last contact date) and to the Post While on Treatment period (interval of time which begins on the last day of treatment + 8 days and ends on the last contact date) (as it is summarized below).

Proven/Probable IFIs Due to All Pathogens During Follow-Up (All Randomized Subjects)

			DRC-Adjudicated Invasive Fungal Infections				
	Proven		Probable		Proven/Probable		Proven/Probable
Study Period	POS	FLU	POS	FLU	POS	FLU	Total
Post Primary Time Period[a]	2	7	2	8	4	15	19
Post While on Treatment[b]	8	8	4	12	12	20	32

During the Post Treatment Phase POS was superior to FLU with regard to the reduced incidence of proven or probable IFIs with a P-value 0.0089.

Analysis of study 316

For each day of blood sampling, a mean composite concentration-time profile of posaconazole was constructed using all concentration-time points collected from subjects on the same day. Plasma posaconazole trough values were to be collected at Weeks 2, 4, 8, 12, and 16 just prior to subjects receiving their posaconazole dose or during the visit done if posaconazole was discontinued earlier.
271 subjects randomized to POS were available at several time points postdose on sample days ranging from Day 2 to Day 138.

The median posaconazole C_{max} for non-IFI while on treatment was 1360 ng/ml (n=241) versus 635 ng/ml (n=5) for those with proven/probable IFI while on treatment. The plasma levels in GVHD subjects with no proven/probable IFI were affected by the type of GVHD, as chronic GVHD subjects had a ≈58% higher median plasma C_{max} compared to acute. Subjects with diarrhea on the day of pharmacokinetic sampling had a ≈57% lower median plasma C_{max} compare to those with no diarrhea which raised concerns by the CHMP and are discussed below.

The results expressed in Odds Ratio did not meet the predefined criteria of non-inferiority. The MAH addressing this point has indicated that at the time of the study design, the exact rate of IFIs was difficult to estimate, particularly in the GVHD population, since there were no large multicentre trials performed on this population. In the medical literature, the rates of IFIs in subjects undergoing HSCT (5% to 35%) often reflect single-centre experience and different prophylaxis strategies in terms of antifungals and duration of treatment.

The MAH stated that the statistical strategy using odds ratio was devised to account for the unknown overall expected IFI incidence. This methodology allowed evaluating if the incidence of IFI with posaconazole was within 15% of the observed IFI incidence with fluconazole.

The MAH was also asked to substantiate what would 1.22% represent as a fraction of the efficacy of fluconazole based on literature data in patients with GVHD. (Per protocol analysis: -4.25 % with CI 95.01% (-9.81%; **+1.22%)**.

The MAH addressing this point has indicated that because the study included more subjects with allogeneic transplant and a longer treatment duration, the Slavin *et al.* (1995) study[2] was selected as reference to justify the non-inferiority effect observed in study 316. The Placebo and Fluconazole incidence rates in the reference study are 17.6% and 6.6%, respectively, when the associated odds ratio for Placebo vs Fluconazole is 3.03 with a 95% confidence interval (CI) of [1.4, 6.5]. Based on this result, the non-inferiority margin that would retain 50% of this effect would correspond to an odds ratio of 1.18. In study 316, the 95% CI for the observed odds ratio of 0.56 for Posaconazole vs. Fluconazole was [0.296, 1.065]. Since the upper limit of this CI is less than the margin of 1.18 derived from the study comparing Placebo and Fluconazole, it can be concluded that Posaconazole has retained at least 50% of the effect of Fluconazole vs. Placebo. In fact, the actual effect retained is more than 80%.

When expressing the results in terms of difference in incidence rates, the point estimate and 95% CI for Placebo minus Fluconazole from the above-mentioned scientific paper, are 10.9%. Based on this, the non-inferiority margin that would retain 50% of this effect would be 1.85%. The upper limit of the per-protocol analysis (1.22%), as referred to by the reviewer, clearly retains more than 50% of the efficacy. In fact, the actual effect retained is 67%. The above arguments support the conclusion that posaconazole is non-inferior to fluconazole.

Given the significant food influence on posaconazole pharmacokinetics (enhanced posaconazole exposure) the use of the drug in patients with digestive GVHD is of particular concern. Indeed, these patients should generally be maintained in the fasted state for a prolonged period (1 month). This is especially critical since, conversely to the recommended posology in the curative indication, the claimed posology in prophylaxis no longer takes into account the ability of the patient to tolerate food or not.

The recommended dosing of oral posaconazole for prophylaxis took into account the common problem of anorexia, nausea, and vomiting associated with cytotoxic chemotherapy and with gut dysfunction related to GVHD. The recommendation to administer posaconazole oral suspension three times daily was designed deliberately to optimize the exposure in this high risk population using the available data from studies in healthy volunteers and in patients. Exposure to posaconazole after a single dose was increased by about 2.6-fold when given with a nutrient supplement and by about 4-fold when given with a high-fat meal. In fasted healthy subjects, the bioavailability of a total daily dose of posaconazole 800 mg was increased by 1.7-fold when the dose was administered as 400 mg BID and by 2.6-fold when the dose administered as 200 mg QID compared to 800 mg administered QD. When the POS dosage for prophylaxis was selected in subjects who potentially might have limited oral tolerability due to underlying disease, a strategy was devised to split the dose to three times a day to coincide with the timing of meals or the administration of a light diet with liquid nutritional supplements to attain the maximum exposure and to optimize compliance.

Analyses to study the impact of gastrointestinal dysfunction could not be performed as requested due to limitations in data collection. The presence of gastrointestinal GVHD was not captured specifically but was included as part of the score for grading GVHD. The individual signs or symptoms of GVHD are recorded in the adverse events module. Diarrhoea and vomiting were more commonly reported as adverse events in subjects with acute GVHD as compared to those with chronic GVHD (29 vs 6 subjects, respectively)

While on treatment in study 316, those subjects who had diarrhoea reported as an adverse event on the day of PK sampling (n=36) had lower median C_{avg} values than subjects with no reported events of diarrhea (718 vs 1009 ng/mL). In contrast, vomiting had less impact on posaconazole plasma levels. There was no difference in POS exposure with or without vomiting (median C_{avg}, 872 vs 922 ng/mL, respectively), most likely because subjects were instructed to repeat their POS dose after emesis was controlled.

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[2] Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR, *et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation--a prospective, randomized, double-blind study.* J Infect Dis 1995: 171 p1545-52.

Overall, although lower levels were seen in subjects with diarrhoea in the setting of acute GVHD, fewer breakthrough IFIs were seen in posaconazole subjects when compared with subjects receiving a highly bioavailable drug (fluconazole). Therefore, even in the presence of clinically significant gastrointestinal dysfunction, the oral administration of posaconazole was well tolerated and resulted in adequate protection against *Aspergillus* and *Candida* infections.

ii. Results of Study 1899

Patient population /Demographic notes

Six hundred and two subjects were randomized. 304 subjects were randomised to posaconazole, 240 to fluconazole and only 58 to itraconazole.

The mean age was 49 years in the posaconazole group, and 50 years in the fluconazole/itraconazole group. As with study 316, most subjects were Caucasian, but in contrast only 52% were male in the posaconazole group (54% in fluconazole/itraconazole group). The majority of subjects (63%) in both treatment arms were neutropenic at baseline; in 24% of subjects, the level of neutropenia was severe (≤100 cells/mm3). In both treatment arms, the majority of subjects (70% posaconazole, 74% FLU/ITZ) had a primary diagnosis of new Acute Myelogenous Leukemia (AML); the remaining subjects were divided fairly evenly between relapsed AML and (Myelodysplastic Syndrome) MDS. The two treatment groups were also similar with respect to the remaining baseline characteristics evaluated. 4% subjects in each arm) had an Aspergillus antigen test reporting a galactomannan index (GMI) of ≥0.5 at baseline. Slightly less than half of the study population had a positive fungal colonization status (assessed from stool/throat culture). Fourteen percent of subjects received systemic antifungals as prophylaxis prior to randomization; the mean duration of prophylaxis was 4 days in the posaconazole arm and 3 days (SD 5.4) in the fluconazole/itraconazole arm. The type of chemotherapy was generally balanced between groups. The use of myeloid growth factors during the treatment phase was similar between the treatment groups, being received in around half of patients.

There were 16 patients aged under 18 in this study, 8 per group.

Disposition of subjects

In study 1899, 52% subjects in the posaconazole arm and 42% subjects in the in fluconazole/itraconazole group completed the treatment Phase.

As already stated a total of 602 subjects (304 POS, 240 FLU, 58 ITZ) were randomized, and 590 subjects were exposed to study medication. One subject in the POS arm received one dose of IV study medication Amphotericin B (AMB) only. This subject was also excluded from the Modified Intent-to-Treat (MITT) subset, which is comprised of 589 subjects who received at least one dose of oral study medication.

	Number (%) of Subjects[a]	
Data Set Analyzed	POS	FLU/ITZ
All Randomized (n=602)	304 (100)	298 (100)
- Not treated with oral study drug	7 (2)	6 (2)
MITT (n=589)	297 (98)	292 (98)
- Did not meet entry criteria[b]	0	1 (<1)
- Non-compliance with study conduct[c]	17 (6)	17 (6)
- Unacceptable concomitant medication[d]	1 (<1)	1 (<1)
- Non-compliance with study treatment[e]	18 (6)	13 (4)
Efficacy Evaluable (n=528)	265 (87)	263 (88)

a: Percentage of subjects is based on the All Randomized Subjects population.
b: Includes subjects who did not have a diagnosis of AML or MDS, or subjects who did not receive intensive chemotherapy expected to result in prolonged neutropenia.
c: Includes subjects who did not have at least 7 days of neutropenia (ANC >500 cells/mm3), or subjects who received >3 consecutive days or ≥10 cumulative days of IV alternative antifungal study medication.
d: Includes subjects who received medications known to lower the serum concentration of azole antifungals for 5 or more days concurrently with study drug.
e: Includes subjects who received <4 consecutive days of oral study drug.

Treatment Phase has consisted of 3 visits (Visits 2 to 4 up to the end of treatment). Visit 2 was conducted on the day the subject began study drug therapy as randomized, before the first dose. For each cycle of chemotherapy, a new cycle number was used to designate the first, second, or third cycle of prophylaxis. Subjects started the study drug after completing the anthracycline component of each cycle. Subjects may have continued on study drug with each cycle of chemotherapy until complete remission or other protocol-specified endpoints were reached, for up to a maximum of 12 weeks or 84 calendar days from randomization.

Then Follow-up Phase has been performed with Visit 5 and Visit 6 (30 days after last dose date for safety and 100 days after randomization date for survival [all cause mortality and fungal-infection-related mortality] and IFI occurrence).

The main difference between the reasons for discontinuing the treatment phase is driven by the more important rate of treatment failure in the FLU/ITZ arm (39% versus 26% in the POS arm).

The population mainly consisted of AML new diagnosis (≈70%), Caucasian subjects (≈75%), balanced number of male/female, subjects weighing approximately 70-75 kg, European patients (≈40%). At baseline (date of randomization: D-7 – D0), only 24% of patients presented severe neutropenia. However, this percentage greatly increased at post-baseline: 87-88% in both arms due to chemotherapy cycle(s) performed for the period of POS administration.

Overall the population enrolled was representative of the population targeted in clinical practice in this indication. The limited population with MDS reflected the more limited resort to prophylaxis in these patients as compared to patients with AML.

The assessment of the comparability of treatment arms (POS vs FLU/ITZ) with respect to certain post-baseline characteristics that were considered to have an impact potentially on the occurrence of IFIs, was performed.

The median total number of days of neutropenia during the Treatment Phase was similar in both treatment groups (POS, 21 days; FLU/ITZ, 20 days), as well as the median number of consecutive days of neutropenia (POS, 18 days; FLU/ITZ, 17 days). The number of subjects with prolonged neutropenia was also higher in the POS arm (33% vs 26% with FLU/ITZ). This higher incidence of cumulative neutropenia in the POS arm may be explained by the fact that more POS subjects completed the Treatment Phase than did FLU/ITZ subjects (52% vs 42%, respectively), and as such, their days of neutropenia continued to be counted until the end of the Treatment Phase or recovery of (absolute neutrophil count, ANC) ANC (>500 cells/mm^3), whichever occurred first.

Concomitant Medications

During the Treatment Phase the number of subjects who received other Systemic Antifungal Therapy **(**SAFs) as empiric treatment for a suspected/proven IFI was higher in the FLU/ITZ arm (38%) than in the POS arm (27%). The use of other SAFs as empiric treatment of a suspected/proven IFI during a neutropenic episode was also more common in the FLU/ITZ group than the POS group (140.9% vs 32.9%, respectively). Approximately one-half of all subjects received growth factors during the Treatment Phase (POS, 48%; FLU/ITZ, 50%). The median duration of use was slightly longer in the POS arm than in the FLU/ITZ arm; however, this slight difference in duration of growth factor use is not considered to be clinically significant.

The treatment arms were well balanced with respect to the number of subjects who received steroids during the Treatment Phase (POS, 62%; FLU/ITZ, 63%), as well as the duration of steroid use.

Results on the Primary endpoint of Study 1899

Results are presented according to time schedule with 4 periods:

- Oral Treatment Phase, from randomization to 7 days after end of oral study drug. This time period was the focus of the primary efficacy analysis. The distribution of IFIs was the same during the Treatment Phase (randomization to 7 days after last dose of oral or IV study medication) as during the Oral Treatment Phase.
  Treatment Phase, from randomization to 7 days after end of treatment (IV or Oral)
- 100-Day Phase, from randomization to 100 days after randomization.
- Post-Oral Treatment Phase
- Post 100-Day Phase.

Oral Treatment Phase
Thirty-two subjects had DRC-adjudicated **proven/probable** IFIs during the Oral Treatment Phase. The incidence was significantly lower with POS than with FLU/ITZ (2% vs 8%, respectively and P=0.0009).

The incidence of proven and probable IFI with POS during the Oral Treatment Phase was lower than with either comparator evaluated separately (FLU 8%; ITZ 10%).

Analysis of the proven/probable IFIs by pathogens:

The incidence of proven and probable IFIs due to *Aspergillus* was not a pre-specified variable for analysis in this study. *Aspergillus* was determined to be the causative pathogen in 22 of the 32 subjects with proven or probable IFIs during the Oral Treatment Phase. The incidence of proven/probable aspergillosis was also significantly lower with POS vs FLU/ITZ during the 100-Day Phase (1% vs 9%, respectively; P<0.0001).

Contrarily to what happens in the posaconazole arm, IFI due to *Aspergillus* represents the majority of IFI in the FLU/ITZ (80%) as compared to 29% % in the POS arm. This translates the limited activity of FLU on *Aspergillus*. Therefore comparison versus FLU was indeed optimal for the posaconazole arm.

Analysis on FLU/ITZ resistant IFI:

FLU/ITZ resistance was assessed by the DRC for each primary pathogen causing a proven or probable IFI. Twenty-six of the 32 subjects with proven or probable IFIs during the Oral Treatment Phase were infected with pathogens that were considered to be FLU- or ITZ-resistant.

The incidence of FLU/ITZ-resistant proven or probable IFIs with POS was lower than with either standard azole agent, evaluated separately (FLU, 8%; ITZ, 9%).

A higher overall incidence of IFIs was observed when assessed by the DRC, regardless of treatment arm or study period (see table below).

Distribution of Proven and Probable IFI by Time Period and Treatment Group determined by DRC (All Randomized Subjects)

	Number (%) of Subjects				
Time Period[a]	POS (n=304)	FLU/ITZ (n=298)	Difference	95.13% CI for the Difference	P-Value
Oral Treatment Phase	**7 (2)**	**25 (8)**	**-6.09%**	**-9.68% to -2.50%**	
100-Day Phase	**14 (5)**	**33 (11)**	**-6.47%**	**-10.76% to -2.17%**	**0.0031**
Post-Oral Treatment Phase	10 (3)	9 (3)	0.27%	-2.54% to 3.08%	0.8501
Post 100-Day Phase	1 (0)	1 (0)	-0.01%	-0.93% to 0.92%	0.9887

Subjects may have had multiple IFIs occurring in different study periods. The distribution of IFIs was the same during the Post-Treatment Phase as during the Post-Oral Treatment Phase.

The superiority of POS over FLU/ITZ is consistently shown on the most pertinent analyses; Oral Treatment phase (P-value, 0.0009) and to a lesser extent 100-Day Phase (P-value 0.031).

Results on the Secondary endpoints of study 1899

There were 13 subjects (7 POS, 6 FLU/ITZ) who were randomized but never treated. These were regarded as treatment failures. The most common reason for treatment failure was empiric use of a systemic antifungal (SAF) agent for >3 consecutive days during the Treatment Phase (POS, 20%; FLU/ITZ, 26%).

Fungal Colonization

Subjects were examined for colonization at Baseline and once weekly while on therapy. The primary colonizing organism at Baseline in both treatment arms was *C. albicans*. The treatment arms showed a steady decline in subjects colonized with *C. albicans* through Week 6 of therapy. During the same time period, there was a slight increase in the number of subjects colonized with *C. glabrata* while *C. krusei* increased slightly in FLU-treated.

Neutropenia

The standard reporting procedure for clinical trials of the treatment and supportive care of leukaemia is to begin counting days of neutropenia from the start of treatment/study until recovery from neutropenia (defined as a neutrophil value of > 500 cells/mm^3) In this study, approximately 70% of subjects enrolled had newly diagnosed AML and were undergoing their first cycle of standard induction chemotherapy. Randomization appropriately balanced the proportion of patients with a new diagnosis of AML receiving posaconazole (70%) (POS) versus fluconazole (FLU) or itraconazole (ITZ) (74%). Although the numbers of subjects were smaller, the proportion of patients with MDS was slightly higher in the POS group (16% POS vs. 13% FLU/ITZ), as was the proportion of patients with relapsed AML (14% POS vs. 13% FLU/ITZ)

The incidence, severity, and duration of neutropenia were also evaluated post-baseline. Approximately 98% of subjects were neutropenic during treatment in both treatment arms, and of those, nearly 90% had an ANC ≤100 cells/mm^3 recorded as their worst value. The treatment arms were balanced for maximum consecutive days of neutropenia during treatment (mean 20 days POS vs 18 days FLU/ITZ), as well as total number of days of neutropenia (mean 25 days POS vs 23 days FLU/ITZ). There were more subjects in the POS arm with >28 consecutive days of neutropenia than the FLU/ITZ arm (17% vs 12%, respectively). It was also anticipated that subjects with MDS/secondary AML or relapsed AML might have prolonged neutropenia relative to newly diagnosed AML subjects. A specific analysis of those subjects who were not neutropenic at baseline, but developed chemotherapy-related neutropenia, also demonstrated that the maximum consecutive days of neutropenia during treatment was balanced between the arms within the strata.

The number of days of neutropenia observed in this study were consistent with literature reports of duration of neutropenia with standard AML treatment regimens (median 13-23 days depending upon the regimen and growth factor support). Growth factor use (G-CSF or GM-CSF), which affects the number of days of neutropenia and may also affect neutrophil function, was also balanced between the 2 treatment arms, 48% POS vs 50% FLU/ITZ.

In summary, the MAH considered that randomization adequately controlled for potential imbalances related to incidence, severity, or duration of neutropenia that might have influenced the risk of breakthrough fungal infections in each of the treatment arms. The course of the neutropenia in subjects with acute myelogenous leukemia/MDS undergoing therapy was consistent with the published literature.

3 Discussion on Clinical Efficacy

i. Study 316

Study 316 is a phase III randomized double blind, double dummy that confers robustness in the efficacy/safety demonstration. It was aimed to evaluate the safety and efficacy of posaconazole oral suspension vs Fluconazole in the Prophylaxis of Invasive Fungal Infections in High-Risk Recipients of Allogeneic Progenitor Cell Transplantation With Graft-Versus-Host Disease (GVHD).

As regards the population enrolled, only 1% of patients were aged between 13 to <18 years in the POS arm), this represents a significant limitation to support the MAH's claim for an extension of indication in prophylaxis in patients from 13 years of age. Consequently the MAH withdrew the application for the paediatric indication.

The most common underlying disease in each treatment group was chronic myelogenous leukemia. About two-thirds of the subjects randomized had acute GVHD, and almost half of the population enrolled had acute Grade 2 GVHD.

The overall study duration (1459 days) corresponds to a very slow rate of inclusion (mean of 0.14 patient/month). While GVHD is the most common source of transplant morbidity, at least two factors accounted for the slow enrolment observed in study 316. An acceptable explanation has been given by the MAH. First, the protocol was overly conservative in the eligibility criteria by attempting to select a uniform population who received only high dose corticosteroids or anti-thymocyte globulin, at a time when the treatment of GVHD was undergoing a significant evolution. Second, because this study used a double-blind, double-dummy design subjects were expected to tolerate two oral study medications (capsules and suspension). Subsequent protocol amendments attempted to broaden enrolment criteria to include more immunosuppressive regimes while still capturing the highest risk patients.

ii. Discussion on Study 1899

Study P01899 is a randomized, open-label, evaluator-blinded, multicenter study to evaluate the safety and efficacy of posaconazole oral suspension (POS) compared with fluconazole (FLU) or itraconazole (ITZ) in the prevention of invasive fungal infections (IFI) in subjects with prolonged neutropenia due to remission-induction chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes.

Subjects were to be stratified based on their primary diagnosis or condition: new diagnosis of Acute Myelogenous Leukemia (AML); AML in first relapse; or Myelodysplastic Syndrome (MDS) or other diagnoses of secondary AML (therapy related, antecedent hematological disorders).

This study was designed to show statistical non-inferiority or superiority between POS and the standard azole (FLU/ITZ) reference arm. The non-inferiority margin has been justified as representing one third of the activity of fluconazole in prophylaxis. Since itraconazole could also be used as a

comparator, this should also have been justified as regards the activity of itraconazole. Even if validated in the prophylactic indication, fluconazole is known as having a very poor activity on *Aspergillus sp*. Therefore, to some extent, the comparison is optimal for posaconazole, since at least for prophylaxis of aspergillosis, this amounts a comparison versus placebo.

As a reassuring finding given the comparator used, a *superiority* of posaconazole over FLU/ITZ is consistently in the analysis of the primary endpoint. As rather expected given the limited activity of FLU on *Aspergillus*, IFI due to *Aspergillus* represents the majority of IFI in the FLU/ITZ (80%) as compared to 29% % in the POS arm. Of interest, a significant difference (P=0.0209) in favor of POS was observed between the treatment groups with respect to the secondary endpoint of time to fungal-infection-related death.

The standard reporting procedure for clinical trials of the treatment and supportive care of leukaemia is to begin counting days of neutropenia from the start of treatment/study until recovery from neutropenia (defined as a neutrophil value of > 500 cells/mm^3) In this study, approximately 70% of subjects enrolled had newly diagnosed AML and were undergoing their first cycle of standard induction chemotherapy.

The MAH considered that randomisation was adequately controlled for potential imbalances related to incidence, severity, or duration of neutropenia that might have influenced the risk of breakthrough fungal infections in each of the treatment arms. The course of the neutropenia in subjects with acute myelogenous leukemia/MDS undergoing therapy was consistent with the published literature.

Whilst for patients presenting with newly diagnosed haematological malignancy (70%) the prior duration of neutropenia cannot be known, for the others the MAH deviated from the CHMP scientific advice (2001) in not collecting data on duration of pre-existing neutropenia at baseline. This information would have been helpful to better characterise the risk factors of AML/MDS patients in this study. However, as these data were not available and assurance has been given about incidence, severity and duration of neutropenia post-baseline being balanced in both arms, it is considered that the efficacy of posaconazole is *substantiated*.

4 Clinical Safety

For this type II Variation the safety data main emphasis was given to monitor the Adverse Events for this class of Azoles.

i Study 316

Extent of Exposure

The safety evaluation included all 600 randomized subjects.

Adverse Events

The most commonly reported Treatment-Emergent Adverse Events (TEAEs) were fever, diarrhea, nausea, vomiting and cytomegalovirus infection, hypertension, hypokalemia, thrombocytopenia, thrombocytopenia aggravated, platelet count decreased.

The most common Serious AEs (SAEs) were fever, aggravated GVHD, diarrhoea, cytomegalovirus infection, dyspnoea, sepsis, hypotension, thrombocytopenia, and respiratory insufficiency.

Examination of AEs possibly related to the medication received revealed blurred vision, hypocalcemia, GI hemorrhage, hepatic dysfunction, anaemia, thrombocytopenia, and neutropenia.

Hepatic Adverse Events
Within this select AE category, bilirubinemia GGT (gamma-glutamyl transferase) increased, hepatic enzymes increased, hepatic function abnormal, jaundice (8% vs 5%), and SGPT (serum glutamic pyruvic transaminase) increases, were among the most common AEs reported.

Hematologic and Lymphatic Adverse Events
Among the subjects in the POS treatment group reporting treatment-emergent thrombocytopenia-associated AEs (thrombocytopenia, thrombocytopenia aggravated, or platelet count decreased), 10 also reported an AE of TTP (thrombotic thrombocytopenic purpura), HUS (Hemolytic uremic syndrome), or thrombocytopenic purpura aggravated.

Thrombotic Microangiopathy
Although the number of subjects with TTP/HUS in the present study was approximately 4%, less than the value proposed in the literature, an imbalance exists between the numbers of subjects with these disorders in the POS arm versus the FLU arm. An interaction of POS with the immunosuppressant could not be ruled out in these cases, since the occurrence of the AEs (particularly thrombocytopenia) was temporally related to the administration of study drug. Since it is known that POS interacts with (cyclosporine A) CSA via the P450 system, it may be postulated that an elevation in CSA drug levels may trigger TTP/HUS in a small number of subjects, thus explaining the low number of excess cases in the POS arm.

Neurologic Adverse Events
The most common neurologic AEs reported were tremor, insomnia, depression, anxiety, and paresthesia

As a result of the observation of neurophospholipidosis in dogs, neurological examinations were included in the study procedures to screen for any increase in neurological events that might indicate an adverse effect in subjects. Overall, the observed incidence of AEs related to neurological function was similar between the POS (38%) and FLU (37%) groups. This is consistent with the results of additional animal studies and other Phase 2/3 studies, which suggest that neurophospholipidosis does not occur in species other than dogs.

Depression
Depression was equally reported in the POS and FLU groups. However, depression worsened was observed in seven subjects in the POS group and was not observed in any subject treated with FLU. All cases of depression worsened and depression psychotic were reported in the first 30 days after starting POS treatment.

Drug Interactions
Seven subjects in the POS group and four subjects in the FLU group experienced drug interaction AEs that were considered serious. Nearly the entire drug interaction-related SAEs in the POS and FLU groups involved cyclosporine or tacrolimus with one resulting to death.

Other Adverse Events of Special/Clinical Interest
Pulmonary hypertension was observed in two subjects and Pulmonary embolism was observed in six subjects in the POS group and were not observed in subjects on FLU The incidence of hypokalemia was more frequently reported during treatment with POS than during FLU treatment. The incidence of severe/LT hypokalemia was higher in the POS group than in the FLU group.

Deaths
Overall, 160 of the 600 randomised subjects died during the course of the study.

The majority of deaths occurring in this study were determined to be unlikely to be related to study drug treatment in both the POS and FLU treatment arms.

For one death, the events (HUS, impaired renal function, and TTP) and the death were considered to be possibly related to POS treatment.

- This was a 19-year-old Caucasian male with a multiyear history of acute lymphoblastic leukemia. He underwent a peripheral blood stem cell transplant approximately 13 months prior to study drug initiation, and developed chronic extensive GVHD. Medically significant thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) were noted with progressive thrombocytopenia and impaired renal function. Study drug was discontinued due to HUS/TTP. Renal failure secondary to HUS was reported followed by severe respiratory insufficiency. Life threatening multiorgan failure was noted and pulmonary fungal infection was suspected. Blood cultures were positive for *Enterococcus.* The subject died due to multiple organ failure; HUS and TTP were considered contributory.

One death was associated with CSA toxicity and considered as probably related to POS treatment.

- This was a 47-year-old Caucasian female with a multiyear history of non-Hodgkin's lymphoma, underwent peripheral blood stem cell transplant (related, matched) and developed Grade 3 GVHD. During the study moderate elevation of creatinine was reported which lead to discontinuation of study drug on the same day. The cyclosporine level reached 428 UG/L which was felt to be life threatening.
  Life threatening leukencephalopathy, cerebellar herniation, and acute renal failure were reported. The subject died of brainstem herniation with leukoencephalitis likely related to cyclosporine followed by hypertensive crisis.

The significant overall mortality rate observed in this study is rather expected as regards the underlying disease of the targeted population.

ii. Study 1899

Extent of Exposure

The safety evaluation included all 602 randomized subjects.

Adverse Events

Given the small number of subjects in the ITZ arm (n=58) compared to the number of subjects treated with POS (n=304) or FLU (n=240), subsequent analyses and discussions related to safety will be limited to distinctions between POS and the standard azole (FLU/ITZ) group.

The most common TEAEs were fever, diarrhea, hypokalemia, nausea, and febrile neutropenia, vomiting, and abdominal pain, headache, petechiae.

Hematologic and infectious events comprised the most common SAEs (thrombocytopenia, febrile neutropenia, anemia, fever, neutropenia, bacteremia, sepsis, and septic shock).

Cardiovascular Events
QT/QTc prolongation and torsades de pointes are of special interest due to previous reports noted with other azole agents as well as the potential seriousness of the events. "Torsades de pointes" was observed in two subjects one in each arm of the study.

QT/QTc prolongation was considered related to study drug and Syncope was reported more frequently in POS subjects than in FLU/ITZ subjects. Two subjects had treatment-emergent SAEs of syncope that were considered possibly related to POS by the Investigator.

Deaths
The most common causes of death were AEs and disease-related (AML/MDS) complications.

Forty-four deaths occurred during the Treatment Phase. Only three subjects died due to IFI progression during this period.

The majority of deaths were determined to be unlikely related to study drug treatment in both the POS and FLU/ITZ treatment groups. One death was considered possibly related to treatment with POS.

The significant mortality observed in this study as well as in the previous study, is rather expected as regards the underlying disease of the targeted population (AML/MDS).

Risk Management Plan

The MAH has provided a Risk Management Plan, which was assessed.
This RMP proposal consisting of 2 parts:

- Safety specification and Pharmacovigilance Plan
- and Risk minimisation plan.

Safety specification
Two concerns were identified in the safety review of the original MAA: drug interactions due to inhibition of P450 CYP3A4 which may cause adverse effects, and phospholipidosis in preclinical studies phospholipidosis in several tissues including lung.
No additional concerns have been identified in the new indication of prophylaxis for patients with prolonged neutropenia or haematopoietic stem cell transplant recipients.

Pharmacovigilance Plan
The objectives are the assessment of drug interactions, the evaluation of potential signals associated to phospholipidosis, and the continuous assessment of the safety profile of posaconazole by an enhanced pharmacovigilance program.
Phase IV studies will be conducted as follow-up measures in the original application, to assess potential drug interactions and to better understand the impact of hepatic insufficiency on the pharmacokinetics of posaconazole.
The postmarketing programme consists of continuous review of individual cases and periodic review of reports of other sources including literature. Periodic signalling reviews on events of interest will be performed and PSURs will be generated as usual.

Risk minimisation plan
The MAH considered that information in section 4.4 Special warning and precautions for use is sufficient to inform prescribers about both azole class events such as hypersensitivity, hepatic toxicity and QTc prolongation and specific posaconazole adverse events such as drug interactions based on the CYP3A4 metabolism. The drug interactions studies have been planned in the context of commitments: interaction with midazolam, sirolimus, PI +/- ritonavir and atazanavir. Moreover, pharmacokinetics in hepatic insufficiency will be explored.

Pharmacovigilance activities (as described below) will be performed to further identify and assess potential safety issues associated with posaconazole administration. Review will occur at the individual, aggregate and epidemiological level with the goal of assessing the strength of an association between an event and posaconazole. Particular focus will be placed on pulmonary events as a previously agreed follow-up measure.

In addition to the Summary of Product Characteristics, there is no need of minimization measures.

However, as requested by the CHMP, the MAH agreed to provide a revised Risk Management Plan in order to include the monitoring in the ongoing/planned studies of GI bleeding, thrombotic microangiopathy (thrombotic thrombocytopenic purpura (TTP), haemolytic uraemic syndrome (HUS), or thrombocytopenic purpura aggravated) and pulmonary haemorrhage. Results of special event monitoring for clinical trials will be included in the Annual Safety Reports and the Periodic Safety Update Reports.

A revised Risk Management Plan will be submitted to include the safety concerns raised by the CHMP.

Clinical Safety

Safety data issued from the two recent studies (316 and 1899) in high-risk patients are provided to support the prophylaxis of IFIs indication. The study 316 was completed in a double blinded and comparative way and it allows the comparison of two azoles and better description of the posaconazole safety profile against fluconazole.

Review of the AEs data show that diarrhoea, nausea, headache, fever and vomiting are among the most commonly reported treatment-related, treatment-emergent adverse events (TEAEs).
The proportion of subjects reporting AEs associated with hepatic dysfunction was similar in the POS (30%) and FLU (28%) treatment groups in the prophylaxis population. In particular, bilirubinemia, (10% vs 9%), gamma-glutamyl transpeptidase (GGT) increased (7% vs 7%), hepatic enzymes increased (6% vs 7%), jaundice (6% vs 5%), and serum glutamic pyruvic transaminase (SGPT) increased (6% vs 6%) were among the most common AEs observed for subjects in the POS and FLU groups, respectively.

Two cases of torsade de pointes were reported in the pooled prophylaxis population, both subjects were from Study 1899, with one in each treatment arm. In general, POS used as prophylaxis treatment of serious fungal infection in immunocompromised subjects appears to have a low potential for induction of QTc prolongation, similar to that observed with FLU.

Eight subjects in the POS group and 4 subjects in the FLU group experienced drug interaction AEs that were considered serious. Nearly the entire drug interaction-related SAEs in the POS and FLU groups involved cyclosporine or tacrolimus. One subject in the POS group experienced cyclosporine toxicity that had an outcome of death.

The incidence of thrombotic microangiopathy, defined as thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome (HUS) was balanced between treatment groups in the prophylaxis pool: TTP (POS 1% vs FLU 1%) and HUS (POS 1% vs 1%) were reported. All subjects were from the study 316.

Overall, 276 of the 1202 subjects in the prophylaxis pool died during the course of the studies. Of these 276 deaths, 125 were subjects in the POS treatment group, 142 were subjects in the FLU treatment group, and 9 were subjects in the ITZ treatment group. In the POS prophylaxis pool, three deaths were considered as possibly related to treatment with POS. The significant mortality rate observed in this study is rather expected as regards the underlying disease of the targeted population.

5. Overall Scientific Discussion and Benefit/Risk Assessment

2 multi-centre, randomised, parallel-group, active comparator-controlled studies were submitted in support of the proposed prophylaxis indication.

Both studies pre-dated the current CHMP “Points to Consider on the Clinical Evaluation of New Agents for Invasive Fungal Infections” (CPMP/EWP/1343/01) when initiated, but the basic design considerations, particularly the choice and evaluation of primary efficacy endpoints, diagnostic criteria, and the way the study is generally reported, are generally in line with this guidance.

For both studies, the duration of therapy and the duration of follow-up appeared reasonable.
A reasonable justification has also been given for the dose of posaconazole selected in the two prophylaxis studies, based on pharmacokinetic and *in-vitro* considerations. Given the relatively low number of breakthrough infections in the two prophylaxis studies submitted and the size of the available population, it might have been difficult to perform an adequately powered dose-ranging study. The posology for posaconazole used in both studies is as per the proposed SPC.

The choice of comparators was reasonable, with both fluconazole and itraconazole being licensed in several Member States for prophylaxis, at the doses chosen.

Clinical Efficacy

As regards the efficacy results, posaconazole failed to achieve the superiority over fluconazole in the double blind, double dummy study 316.
This study was designed to show statistical non-inferiority or superiority between POS and the standard azole (FLU/ITZ) reference arm. Only the non-inferiority margin has been justified as representing one third of the activity of fluconazole in prophylaxis. Since itraconazole could also be used as a comparator, this should also have been justified as regards the activity of itraconazole.

It is known that fluconazole has a very poor activity on *Aspergillus sp*. Therefore, to some extent, the comparison is optimal for posaconazole, since at least for prophylaxis of aspergillosis, this amounts a comparison versus placebo. Nevertheless, it has to be admitted that at this stage fluconazole is the unique oral antifungal agent to be validated in prophylaxis.

The initial proposal of the wording of the Indication for prophylaxis was very broad. After the assessment of the submitted data and the discussion at the CHMP the MAH has proposed a revised indication to strictly reflect to the population enrolled in these assessed clinical studies for the reason that the population studied in both (316 and 1899) was very precisely characterised.

Furthermore since the clinical data were too limited to enable a proper benefit/risk assessment in children between 13-18 years (in total only 28 patients were enrolled and in a range of different ages) the indication in prophylaxis was restricted in **adult** patients.

The posology recommended in the Summary of Product Characteristics was in line with the patient population studied in the Clinical Studies (316 and 1899) as well as the justification for administration together with food during the treatment. It also takes into account the state of the patients due to the underlying illnesses and it is reflected in the frequency and the duration of the administration.

Clinical Safety

Overall the safety profile of posaconazole was comparable to the one of fluconazole.

Trends for a higher rate of hepatic events, GI bleeding thrombotic microangiopathy (thrombotic thrombocytopenic purpura (TTP), Hemolytic uremic syndrome (HUS), or thrombocytopenic purpura aggravated), hypokalaemia and worsening of depression are observed. The MAH has taken the obligation to closely observe these findings and include them in the revised Risk Management Plan.

The MAH stated that the imbalances in these adverse events appeared to be due to known complications of pre-existing conditions that were not completely controlled by stratification and randomisation as well as the contributing influences of additional therapies with known side effects also could not be controlled through the randomization process. This in many cases could be accepted as justification.

The Risk Management Plan was submitted and will be updated as requested by the CHMP to reflect the findings in safety of the clinical studies assessed.

Benefit/Risk assessment

Taken into account the clinical data on efficacy and safety presented and the MAH commitment for the monitoring regarding safety, the CHMP considered by consensus that the benefit/risk ratio for the proposed indication in prophylaxis in the specific adult population was favourable and therefore recommended the proposed changes in the Summary of Product Characteristics and the Package Leaflet.

6 Changes To The Product Information

- **Summary of Product Characteristics**

Section 4.1 "Therapeutic indication"

The MAH's initial proposed changes to section 4.1 were discussed and not agreeable by the CHMP mainly due to the fact that the indication was too broad and included the paediatric populations.

However, a revised wording was proposed by the MAH for the section 4.1 "Therapeutic Indication" and was considered for the assessment of this variation. The following text was agreed with (the new text added or amended is underlined):

"4.1 Therapeutic indications

Noxafil is indicated for use in the treatment of the following ~~invasive~~ fungal infections in adults (see section 5.1):

- *Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;*
- *Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;*
- *Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;*
- *Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products;*

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

Noxafil is also indicated for prophylaxis of invasive fungal infections in the following patients:

- *Patients receiving remission-induction chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections;*
- *Hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections."*

Section 4.2 "Posology and method of administration"

The MAH initially had proposed a wording on posology for children more that 13 years of age. However since this indication was not been accepted by the CHMP for the reason described above, it was eventually withdrawn from the SPC.

For the concluded indication of Prophylaxis in adults the wording in this SPC section is as follows:

"Prophylaxis of Invasive Fungal Infections	*200 mg (5 ml) three times a day. Each dose of Noxafil should be administered with a meal, or with a nutritional supplement in patients who cannot tolerate food to enhance the oral absorption and to ensure adequate exposure.* *The duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia or myelodysplastic syndromes, prophylaxis with Noxafil should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm^3."*

There are limited pharmacokinetic data in patients with severe gastrointestinal dysfunction (such as severe diarrhoea). Patients who have severe diarrhoea or vomiting should be monitored closely for breakthrough fungal infections.

The oral suspension must be shaken well before use.

- **Other changes in the Summary of Product Characteristics**

The Section 4.8 "Undesirable effects" of the SPC was updated to include the safety information derived from the two clinical studies assessed. The revision takes into account the Adverse Events reported and their frequency.

The revision of the Section 5.1 "Pharmacodynamic properties" of the SPC includes the description and the results of the studies assessed.

The changes in the Section 5.2 "Pharmacokinetic properties" of the SPC also reflects the new data presented in support of the new indication.

Consequential changes have also been introduced in the sections 4.4 "Special warnings and precautions for use" distinguishing between events observed and their frequency, 4.5 "Interaction with other medicinal products and other forms of interactions".