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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, the advent of highly active antiretroviral therapy (HAART) and associated declining incidence among HIV patients has limited market growth.

Posaconazole (POS) 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 Marketing Authorisation was approved in October 2005.

Candidiasis in the oropharynx is a very common fungal infection, and is the most common opportunistic infection in HIV-infected patients, the population studied in this submission. In these patients, oesophageal candidiasis is also a significant and difficult to treat problem.

Generally, the initial treatment for oropharyngeal candidiasis might be with nystatin, amphotericin or miconazole given topically. Fluconazole or itraconazole might be tried orally for unresponsive infections. For immunocompromised patients, or patients with severe or recurrent oropharyngeal

candidiasis, initial oral treatment would be more appropriate, and first-line use is covered in the current licensed indications for both fluconazole and itraconazole.

The initial treatment for oesophageal candidiasis would generally be systemic azole antifungals such as fluconazole and itraconazole.

The current options for oropharyngeal or oesophageal candidiasis in patients with disease already refractory to itraconazole and fluconazole are limited.

Through this type II variation the MAH initially applied to extend the therapeutic indication to include oropharyngeal candidiasis as well as for oesophageal candidiasis. Further to the preliminary assessment of the submitted data, the latter indication was no longer pursued.

Consequently this Assessment Report focuses on the treatment of oropharyngeal candidiasis as the proposed indication for assessment.

2 Non clinical aspects

No new non clinical data has been provided in support to the request of extension of indication.

3 Clinical aspects

3.1 Bioequivalence and Bioavailability Studies

Pharmacokinetics

A bioequivalence study with posaconazole (POS) oral suspension (P03409) was conducted to assess the feasibility of changing the drug product particle size, comparing two oral suspensions differing in median particle size (2.3 µm versus 1.7 µm, reference), in the context of possible future manufacturing scale and equipment changes. The POS suspension was used because some patients were unable to swallow the capsules.

This study is presented by the MAH to support the choice of the posaconazole presentation used in the main studies (described later) in support of the orophangyeal Candidiasis indication.

Also, a relative bioavailability and bioequivalence study (C90-180) was conducted with Diflucan (fluconazole) encapsulated commercial tablet vs Diflucan commercial tablet. This study was performed in order to assist to the blinding of the following clinical studies submitted to support the change of the indication claim, described below.

Study P03409

Design

In theory, changes to the particle size of a drug in suspension alter the surface area, which may result in changes of the rate of dissolution and ultimately of the rate and extent of absorption. Therefore, this bioequivalence study was conducted to see whether this small increase in median particle size affects the oral bioavailability of the posaconazole suspension.

Approximately 40 healthy male and female subjects were planned to be enrolled. Subjects were to receive a single dose of the reference treatment on two occasions and a single dose of the test treatment on two occasions.

To minimise the impact of variability of POS pharmacokinetics on the assessment of bioequivalence, a replicate, crossover design was chosen for the study. Treatment sequence for each subject — either ABAB or BABA — was determined according to a randomisation code.

The single dose of 400 mg was chosen as the recommended clinical dose for the treatment of invasive fungal infections (400 mg BID of the suspension). POS 400 mg was given in the morning after a high-fat breakfast as it was found that food consumption was a critical factor that affected the bioavailability of POS. Administration of POS with a non-fat meal or a high-fat nutritional supplement (~14 gm fat) resulted in 2.6 times higher exposure relative to the fasted state, while administration with a high-fat meal (~50 gm fat) resulted in 4 times higher exposure. Thus, in order to maximise exposure, it was recommended that POS be administered with food or a nutritional supplement.

A single dose of POS was administered on Day 1 of each 7-day treatment period for four periods. Each period was 7-day treatment followed by at least 14 days washout period between the treatment administrations. Subjects were confined to the study site from Day -1 until the morning of Day 4 in all four-treatment periods. The duration of the study was approximately 60 days. Subjects returned to the site for three outpatient visits on Days 5, 6, and 7.

For POS suspension with median particle size 1.7 µm, the dissolution data indicated that an average of 97% of the suspension dissolved in 30 minutes vs an average of 89% for test product. The content uniformity data indicated an average of 103.8% labelled strength vs an average of 100.8% respectively.

Methods

Blood samples for the determination of plasma POS concentrations were obtained prior to the first morning dose (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours postdose in all periods. The 96-, 120-, and 144-hour blood samples were to be collected on an outpatient basis. Plasma sample analysis for POS was performed by using a validated liquid chromatography with mass spectrometric detection (LC-MS/MS) method.

The primary pharmacokinetic endpoints were C_{max} and AUC.

Bioequivalence was assessed by the 90% confidence intervals (90% CI) for the difference between two treatments. There were no amendments to the protocol.

Results

Twenty-one subjects were included in each of the treatment sequences: ABAB or BABA. Eighteen subjects completed treatment sequence ABAB and 21 completed treatment sequence BABA. Three subjects discontinued from the study (ABAB sequence) mainly due to possibly drug related Adverse Events.

With the exception of AUC(I), which could not be determined in one subject, pharmacokinetic analysis was conducted on the data for all 39 subjects who completed the four treatment periods. All 42 randomised subjects were included in the safety analysis.

The relative bioavailability of the large (2.3µm) particle size batch compared with the small (1.7µm) particle size batch was 76% with 90% confidence interval (CI) limits of 65-88%

The intrasubject and intersubject variability appeared to be higher for the large particle size test product compared with that for the small particle size reference product. For the small particle size reference product, the intrasubject variability was lower than the intersubject variability, as would typically be expected. The intrasubject variability for the large particle size test product was greater than the intersubject variability.

Intersubject and Intrasubject Variability (Variance Estimate Based on Log-Transformed Data)

Parameter	Intersubject Variability		Intrasubject Variability	
	B	**A**	**B**	**A**
C_{max}	0.17	0.09	0.20	0.07
AUC(tf)	0.19	0.13	0.23	0.07
AUC(l)	0.19	0.13	0.22	0.07

Although the analysis did not reveal any statistically significant sequence or period effect, the geometric means of AUC values for the subjects who received the small particle size batch in periods 1 and 3 appeared higher than those for the subjects who received the small particle size batch in periods 2 and 4.

In contrast, the geometric means of AUC values for the large particle size suspension were relatively consistent no matter which sequence (ABAB or BABA) the subject was enrolled into.
While treated with the large particle size suspension, 4 subjects had consistently (i.e., replicated) low AUC values with low AUC ratio estimates for large particle size relative to small particle size (0.17 to 0.39), but did not meet the statistical criteria to be considered outliers and cannot be excluded from the analysis. Therefore, high AUC values for subjects administered the small particle size batch in periods 1 and 3 and consistently low AUC values for four subjects in the large particle size group may have in part contributed to the observed difference in bioavailability.

Conclusion of study P03409

Following the analysis of the results of this study (P03409) it was shown that POS suspension with a median particle size of 2.3 µm is not bioequivalent to POS suspension with a median particle size of 1.7 µm. The relative bioavailability of the large particle size suspension was 76% of the small particle size suspension.

The fact that the two different sized POS suspensions are not bioequivalent, has to be taken into account in the context of possible future manufacturing scale and equipment changes.

Unfortunately no studies have been performed to further investigate the bioequivalence of the POS suspension and the POS capsule.

Study C90-180

Design

This study was designed to compare the bioavailability/bioequivalence of the commercially available Diflucan tablet to a Diflucan encapsulated tablet. The latter was the intended formulation to be used for blinding purposes in comparative studies with POS. Bioequivalency of the Diflucan tablet and Diflucan encapsulated tablet would allow the results and conclusions obtained from the encapsulated tablet to be applied to the commercially available tablet formulation.

Each subject alternately received a single dose of 50 mg Diflucan as a tablet and as an encapsulated tablet, in an order determined by a computer generated randomisation schedule. A washout period of two weeks was observed between the treatments.

Conclusion of study C90-180

The pharmacokinetic parameters of fluconazole were similar between the 2 formulations. The relative bioavailability of the Diflucan encapsulated tablet was 100% based on AUC(tf) and AUC(I) values, and 102% based on C_{max} values. The 90% confidence interval for the AUC and C_{max} values were both within the range satisfying the criteria for bioequivalence (between 80% to 125%).

Therefore, it can be concluded that the Diflucan encapsulated tablet was bioequivalent to the commercially available Diflucan tablet. Results obtained with Diflucan encapsulated (for blinding

purpose) in clinical studies could then be applied to the commercially available tablet of Diflucan. Results obtained with Diflucan encapsulated (for blinding purpose) in clinical studies could then be applied to the commercially available tablet of Diflucan.

3.2 Clinical Efficacy

Pharmacokinetics

The main data to support the claimed indications comprises four clinical studies (C/I97-209, C/I97-331, P00298, C/I97-330), all in HIV patients ≥ 18 years of age. For brevity they will be referred as studies 209, 331, 298 and 330 in the report.

Study designs

Azole susceptible oropharyngeal candidiasis

Study 331 is pivotal for the claim in azole susceptible oropharyngeal candidiasis; this was preceded by the dose-ranging study 209. Between these 2 studies, there were 260 patients (MITT subset) treated with the proposed 100 mg daily dose of posaconazole, and 243 patients available for comparison receiving fluconazole.

Study 209 was (a dose finding study) a Phase II, double-blind study comparing posaconazole (400 mg twice daily on day 1 and then 50, 100, 200 or 400 mg daily) and fluconazole (200 mg on day 1 and then 100 mg daily) in HIV-infected patients with oropharyngeal candidiasis with the objective to show that the highest dose was shown to be at least equivalent to FLU and to assess the clinical response at the end of the 14-day treatment phase.

Azole refractory oropharyngeal candidiasis/oesophageal candidiasis

Study 330, the pivotal study in patients with non-refractory oropharyngeal candidiasis, was a randomised, active comparator study with evaluator blinding only. It was a Phase III, randomised, multicenter, evaluator-blinded study in HIV-infected patients with oropharyngeal candidiasis

Study 298 was a Phase II, open-label, non comparative trial of posaconazole in the treatment of azole refractory candidiasis in HIV-infected subjects, while the study 330 was a Phase III, open-label, non comparative trial of posaconazole in the treatment of azole refractory candidiasis in HIV-infected subjects.

Studies 330 and 298 are pivotal for the claims in oropharyngeal candidiasis/ oesophageal candidiasis, in patients with disease refractory to itraconazole and fluconazole. Study 330 enrolled 199 patients, of which 176 featured in the primary analysis set (MITT analysis set, patients with evidence of azole refractory candida culture at baseline). Of these, 43 had azole-refractory oesophageal candidiasis, either alone or in combination with oropharyngeal candidiasis. Study 298 was very similar but included a maintenance treatment phase. This enrolled 100 patients, of which 60 (including 15 with azole-refractory oesophageal candidiasis) had been previously treated in Study 330. The MITT analysis set contained 90 patients.

All the 4 clinical studies submitted in oropharyngeal and oesophageal candidiasis were in HIV-infected adults ≥18 years of age.

The 2 studies in patients with refractory disease, studies 330 and 298, were however open-label and uncontrolled.

Justification for posaconazole dose in azole-susceptible patients (study 331)

In study 331 the dose of posaconazole suspension was 200 mg on day 1, followed by 100 mg QD on days 2-14. This was compared against fluconazole suspension, 200 mg on day 1, followed by 100 mg QD on days 2-14.

The dose in study 331 was based on the previous dose ranging study 209. In this study, posaconazole 800 mg for one day followed by 100 mg QD for 13 days was the lowest efficacious dose. No clear clinical dose response was observed for posaconazole 50 mg, 100 mg, 200 mg, or 400 mg QD. It was felt that this was due to use of the same high loading dose (400 mg BID) of posaconazole in each group, particularly given the long half-life of the drug. The 400-mg and 100-mg doses of posaconazole were clinically equivalent and similar to fluconazole in the proportions of subjects with clinical success (cure or improvement) in both the MITT and per-protocol subsets. The 50-mg dose of posaconazole was also equivalent to fluconazole in the MITT subset using the same criteria; however, this was not the case in the per-protocol subset. The posaconazole dose of 100 mg was chosen as the optimal dose from the standpoint of efficacy, since the clinical response rate for the 50-mg posaconazole dose was not statistically equivalent to fluconazole 100 mg across all datasets examined. The clinical success rate for the 200-mg dose was the lowest of all treatment groups and was not clinically equivalent to fluconazole in either data set. No dose-response was observed for posaconazole 50 mg, 100 mg, 200 mg, and 400 mg based on mycological success rates (≤20 CFU/ml) for the MITT subset of subjects at treatment endpoint.

Dose regimen in refractory patients (studies 330 and 298)

In study 330 the original dosing schedule was posaconazole 400 mg BID x 3 days, then 400 mg QD x 25 days, with a maintenance phase of 400 mg BID three times weekly for 3 months. In an amendment to the protocol an amended schedule of posaconazole 400 mg BID for 28 days was introduced. The reason was that clinical relapse rates 4 weeks after the last dose of POS were lower for subjects treated with 400 mg BID (24.6%) than for subjects treated with 400 mg QD (32.8%), suggesting better and more sustained efficacy with the 400 mg BID daily dosing regimen compared to the 400 mg daily dosing. The maintenance period included in the original protocol was discontinued; study 298 was initiated instead to look at long-term treatment.

In study 298, looking at a long-term treatment, the posology was posaconazole 400 mg BID for up to 15 months; administered as oral suspension (treatment phase of up to 3 months, with 1-month follow-up for subjects with clinical cure, followed by maintenance phase of up to 12 months for subjects who relapsed in follow-up or showed improvement after treatment phase)

Efficacy endpoints

Azole susceptible oropharyngeal candidiasis

The *primary efficacy* variable in the two azole-susceptible OPC studies (studies 209 and 331) was the clinical success rate. This was defined as the number of subjects with a cure (absence of pseudomembranous plaques/ulcers and no, or minimal, symptoms) or improvement (partial resolution of pre-treatment signs and symptoms) at end of therapy (after 14 days of treatment) in the MITT subset. The MITT subset consisted of all randomised subjects with a positive *Candida* culture at Visit 1 (baseline) who had taken at least one dose of study drug.

Posaconazole was considered equivalent to FLU if the lower limit of the confidence interval for the difference in the corresponding response rates (POS-FLU) exceeded a delta of -15%, if the observed rate for FLU was greater than 80% and exceeded a delta of -20%, and if the observed rate for FLU was 80% or less.

A scale from a modified AIDs Clinical Trial Group (ACTG) protocol was used to evaluate signs of mucositis/oesophagitis (plaques or ulcers) at each visit as follows:

0 None = Absent
1 Minimal = 1 to 5 discrete plaques and/or one confluent plaque ≤3 cm in longest length
2 Diffuse = Plaques that were more than minimal extent
3 Worse = Plaques were clearly worse than on previous visit. (Applied only to Visits 2 and 3 in subjects with diffuse plaques on the previous visit.)

Symptoms of mucositis were rated as follows:

0 None = Symptom was not present
1 Mild = Symptom was present, but no or minimal interference was noted with eating
2 Moderate = Symptom(s) present, which led to interference with eating many foods
3 Severe = Symptom(s) were very marked. The subject was unable to eat most foods

The *Secondary efficacy endpoints* were:

- Clinical response after 7 days of treatment (compared to that achieved after 14 days fluconazole)
- Rate of clinical relapse 4 weeks after last dose of study drug
- Mycologic response
  After 7 days of treatment
  At the end of treatment (major timepoint for this analysis)
  At the end of follow-up (1 month after end of treatment)

Mycological response was evaluated according to the following definitions:

- Eradication (Mycological success): ≤20 CFU/mL *Candida* species
- Persistence (Mycological failure): >20 CFU/mL *Candida* species
- Relapse: ≤20 CFU/mL *Candida* species at Visit 3 and >20 CFU/mL at Visit 4
- Superinfection: A *Candida* species present at Visit 3 (end of treatment), but not at baseline
- New Infection: A *Candida* species present for the first time at Visit 4
- Indeterminant: Extenuating circumstances preclude classification

Azole refractory oropharyngeal and/or oesophageal candidiasis

The *primary endpoint* in studies 298 and 330 was also clinical response. For study 330, the primary timepoint was the end of the 4-week treatment period, for study 289 the primary timepoint was the end of the 3-month acute treatment period. This was scored in a similar way to study 331, and the definition of clinical success was also subjects who were cured or improved based on these scales.

For study 330, in subjects with suspected oesophagitis, an oesophagoscopy was performed at the initial visit and at the 4-week visit. Following a protocol amendment it could be performed at the 2-week point if clinically indicated. In study 298, oesophagoscopy was obtained at visit 1 only for patients with symptoms of oesophagitis, and for patients with oesophagitis who failed therapy or relapsed.

Secondary efficacy endpoints included mycologic response (evaluated as per study 331) and measures of relapse rate.

Patient population

Azole susceptible oropharyngeal candidiasis

Study 331
The key inclusion criteria were:

- HIV positive patients with clinical evidence of pseudomembranous Oropharyngeal Candidiasis at time of enrolment into the study

- Laboratory evidence of candidiasis documented by fungal stain of scraping positive for yeasts, hyphae or pseudohyphae that was consistent with *Candida* species, and subsequently confirmed by a positive mycologic culture

Exclusions for enrolment included history of treatment failure with fluconazole (100 mg/day for 2 weeks in the last 3 months) and prior use of Posaconazole in the preceding 3 months.

In both studies of azole-susceptible Oropharyngeal Candidiasis, the two treatment groups were generally similar for baseline demographic and disease characteristics. In the main study 331, the median CD4 (clusters of differentiation 4 antigen) count was 82 cells/mm^3 in the posaconazole group (MITT subset) and 71 in the fluconazole group, although it varied widely.

Also in study 331, the MIC values confirmed that this was an azole-susceptible population, based on lack of fluconazole resistance at baseline. This was assessed against 2002 Clinical and Laboratory Standards Institute (CLSI) breakpoints of: susceptible (≤8 µg/ml), dose dependent (>8 µg/ml to ≤32 µg/ml), and resistant (>32 µg/ml). European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for fluconazole are not yet available.

The vast majority of subjects in study 331 had *C. albicans* identified at baseline. A handful of subjects had other *Candida* species (i.e. *C. glabrata*, *C. krusei*, and *C. tropicalis*)

Azole refractory oropharyngeal and/or oesophageal candidiasis

Both studies (298 and 330) included adult HIV-infected subjects with oral and/or oesophageal candidiasis refractory to a standard course of therapy with fluconazole or itraconazole within 3 months prior to enrolment. A standard course of therapy was defined as ≥100 mg/day fluconazole for at least 10 consecutive days, or itraconazole 200 mg/day for at least 10 consecutive days for oral, or ≥3 weeks for oesophageal candidiasis.

Evidence of oropharyngeal candidiasis at time of enrolment had to be accompanied by laboratory stain and confirmed by subsequent culture, as per study 331. Oesophageal candidiasis had to be documented by oesophagoscopy or oesophageal biopsy/brushing and culture.

Study 298 included subjects who were previously treated under study 330 and who had incomplete resolution of disease or subsequently relapsed.

In study 298, 59 of the 90 subjects in the MITT subset were enrolled and previously treated with posaconazole under study 330 and 31 subjects were posaconazole-naïve.

A CD4 count was available for most patients at baseline in study 330 – the median value was around 10 cells/mm^3, as would be expected this was significantly lower than the median value in the non-refractory patients (82 cells/mm^3), in study 331.

Overall, in the MITT subset for studies 330 and 298 the mean baseline MIC was 44 for fluconazole, 2.7 for itraconazole, the baseline MIC_{50} results for any *Candida* isolate were 64 mcg/ml for fluconazole and 0.5 mcg /ml for itraconazole.

As above, for fluconazole the breakpoint for resistance is >32 µg/ml. For itraconazole the values are: Sensitive ≤0.125 mcg/ml, Sensitive/dose-dependent 0.25-0.5 mcg/ml, resistant ≥1 mcg/ml. The efficacy results were analysed by baseline resistance, as discussed below.

The baseline species found are given in the following table:

Fungal culture at baseline – MITT subset

Candida Species	**Study 298,** (n=90)	**Study 330**, (n=176)
C albicans	68 (91%)[i]	100 (58%)
C glabrata	24 (32%)	25 (14%)
C krusei	3 (4%)	10 (6%)
C tropicalis	2 (3%)	3 (2%)
Other species	2 (3%)	1 (1%)

[i] Percentages are based on the number of subjects with a baseline culture greater than 20 CFU/mL
Some subjects may have had more than one isolate and thus may be included in more than one of the culture categories.

Disposition of subjects and extent of exposure

In study 331, 89% of subjects who received study drug completed treatment. In total there were 350 patients: 157, 153 for POS & FLU respectively as per the table below. At end of therapy, clinical response rates were very similar between treatments in the MITT (92% per group) and evaluable (97% and 96% per group) populations. Fewer patients in the posaconazole group had relapsed by the follow-up at week 4 post-therapy (59% vs 74% in both populations).

Disposition of subjects in study 331

Final Status	Posaconazole 100 mg (n=178)	Fluconazole 100 mg (n=172)
Number (%) of Subjects Who Completed Treatment	**157 (88)**	**153 (89)**
Number (%) of Subjects Who Discontinued Treatment	**21 (12)**	**19 (11)**
Adverse event	7 (4)	6 (3)
Treatment failure	3 (2)	3(2)
Lost to follow-up	3 (2)	4 (2)
Subject decided not to continue treatment	1 (<1)	0
Noncompliance	5 (3)	3 (2)
Did not meet protocol eligibility	2 (1)	3 (2)
Completed Follow-Up	**150 (84)**	**141 (82)**
Discontinued Follow-Up	**28 (16)**	**31 (18)**
Did not enter follow-up	16 (9)	14 (8)
Adverse event	3 (2)	4 (2)
Relapse/recurrence	2 (1)	5 (3)
Lost to follow-up	3 (2)	6 (3)
Noncompliance with protocol	3 (2)	1 (<1)
Failed to meet study entry criteria	1 (<1)	1 (<1)

In study 330, 74% of subjects completed the acute treatment period. Among the 239 unique subjects treated with posaconazole in the two azole-refractory oropharyngeal candidiasis and/or oesophageal candidiasis studies, 69%, of subjects were treated with posaconazole for up to 3 months, 14% were treated for 3 to <6 months, 9% were treated for 6 to <12 months, and 6% of subjects were treated for at least 12 months. The mean exposure to posaconazole based on the actual days dosed was 102 days (range of 1 to 544 days)

In study 298, 65% of subjects completed the acute treatment phase. 43% of all subjects entered follow-up either immediately following completion of acute treatment or discontinuation from acute treatment, of which 81% completed follow-up.

3.3 Results

Azole susceptible oropharyngeal candidiasis

For the main study 331, posaconazole was *non-inferior* to fluconazole in the primary efficacy parameter, clinical success rate. In the primary MITT subset the percentages of patients with cure or improvement after 14 days of treatment were 91.7% in the posaconazole group and 92.5% in the fluconazole group. The majority of subjects in each group were assessed as cured at this timepoint. Results for the *primary endpoint* were consistent in the protocol evaluable subset.

Study 331: Primary endpoint - Clinical Success After 14 Days of Treatment

	Posaconazole 100 mg		Fluconazole 100 mg	
	Modified Intent-to-Treat[a] (n=169)	Protocol Evaluable (n=143)	Modified Intent-to-Treat (n=160)	Protocol Evaluable[a] (n=135)
Success, number (%) of subjects[b]	155 (91.7)	139 (97.2)	148 (92.5)	130 (96.3)
Cure	138 (81.7)	125 (87.4)	132 (82.5)	116 (85.9)
Improvement	17 (10.1)	14 (9.8)	16 (10.0)	14 (10.4)
Lower Limit of 95.0% Confidence Interval				
Success, % of subjects	87.6	94.5	88.4	93.1
Difference (%)[c]	-0.78	+0.91	–	–

a: Subject No. 161/I-19 (Posaconazole) in the Modified Intent-To-Treat Subset took one dose of study drug that expired during treatment; Subject No. 162/I-18 (Fluconazole) in the Protocol Evaluable Subset took eight doses of study drug that expired during treatment.

b: Success: number of subjects who achieved a cure plus number of subjects who improved.

c: Difference (%) =Posaconazole (%) – Fluconazole (%).

The MAH stated that the clinical response rate in study 331 achieved with posaconazole after 7 days was equivalent to that achieved with fluconazole after 14 days of treatment (in the MITT subsets the figures were 91.7% vs. 92.5% respectively).

This is difficult to interpret without knowing what the response rate was for fluconazole after 7 days of treatment – both treatments might have a good response rate by day 7, half-way through treatment.

Clinical response rates 4 weeks after the cessation of treatment were 68.5% versus 61.8% for posaconazole- and fluconazole-treated subjects respectively – i.e. the relapse rates were lower in the posaconazole group (figures for MITT subset).

Mycological response is given in the table below:

Study 331 - Mycological Response (in subjects with Candida Isolated, MITT subset)

	Visit 2 (After 7 Days Treatment)		Visit 3 (After 14 Days Treatment)		Visit 4 (End of Follow-up)[b]	
Visit[a]	Posaconazole 100 mg (n=169)	Fluconazole 100 mg (n=160)	Posaconazole 100 mg (n=169)	Fluconazole 100 mg (n=160)	Posaconazole 100 mg (n=101)	Fluconazole 100 mg (n=91)
Success, number (%) of subjects	100 (59.2)	83 (51.9)	115 (68.0)	109 (68.1)	41 (40.6)[c]	24 (26.4)[c]
Eradication, number (%) of subjects	84 (49.7)	72 (45.0)	102 (60.4)	93 (58.1)	36 (35.6)	22 (24.2)

a: Results for other data subsets was consistent
b: For subjects with follow-up data.
c: MAH quotes P=0.025 for this comparison – however no adjustment was made for multiplicity.

Subjects treated with posaconazole had a greater mycological success rate 4 weeks following cessation of treatment than did subjects treated with fluconazole (40.6%, versus 26.4%, respectively; P=0.0376).

There was no difference in the treatment arms with respect to the antiretroviral therapy at the baseline study 331 (37% of POS-treated subjects and 30% of FLU-treated subjects received anti-retroviral therapies).

In view of current therapeutic guidelines, it is rather unexpected that a significant number of patients with CD4<200 cells/mm^3 (inclusion criteria) were not receiving HIV therapies.

Is Study 209 there was no apparent dose response relationship for clinical success rates between posaconazole doses (85%, 87%, 77%, 87% for 50, 100, 200 and 400 mg respectively) and these rates were similar to that for fluconazole (89%). However, the corresponding mycological eradication rates were 36-40% for posaconazole from 50 mg to 400 mg and 51% for fluconazole.

Azole refractory oropharyngeal and/or oesophageal candidiasis

Studies 330 and 298 assessed the use of posaconazole in HIV patients with oropharyngeal and/or oesophageal candidiasis with disease refractory to itraconazole and fluconazole. The patients had advanced HIV disease as is clear from the low average CD4 count.

Primary endpoints

The *primary endpoint* in study 330 was clinical response at the end of the 4-week treatment period. For this endpoint, in the primary MITT subset, a 75% clinical success rate (either cured or improved, 53% were cured). Clinical success rate was generally similar in subjects with documented baseline microbiological resistance to fluconazole and/or itraconazole, both for subjects with *C albicans* isolates and in the smaller number with other isolates (see table below)

Clinical Response Rates for Any Candida and Candida albicans Baseline Isolates: *Number (%) of Clinical Responders by Baseline Fluconazole and/or Itraconazole MIC Values Based on the CLSI MIC Breakpoints – Modified Intent-to-Treat Subset*

MIC Breakpoints (µg/mL)[a]		Any *Candida*		*Candida albicans*	
		n[b]	Number (%) of Responders	n[b]	Number (%) of Responders
Fluconazole:					
Susceptible	≤8	33	30 (91)	37	35 (95)
Dose Dependent	>8 to ≤32	45	37 (82)	45	35 (78)
Resistant	>32	92	67 (73)	71	51 (72)
Itraconazole:					
Susceptible	≤0.125	41	37 (90)	46	41 (89)
Dose Dependent	>0.125 to <1.0	62	47 (76)	62	48 (77)
Resistant	≥1.0	66	49 (74)	44	31 (70)
Combination of Fluconazole and Itraconazole:					
Dose Dependent or Resistant	Fluconazole >8, Itraconazole >0.125	115	84 (73)	93	66 (71)
Resistant	Fluconazole >32 Itraconazole ≥1.0	57	42 (73)	37	25 (68)

a: Results other than a standard concentration value are assigned to the next higher standard concentration value. If a subject has multiple values within an organism, the maximum value within that species was used.

b: Number of subjects with a baseline MIC value that met the specified criteria.

The *primary endpoint* in study 298 was clinical response at the completion of the 3-month acute treatment period. In the primary MITT subset, a 85.6% clinical success rate was achieved after 3 months of posaconazole treatment. However this percentage included patients either cured or improved, without indicating the percentage of the cured patients. When subdivided into posaconazole

treated (patients who had previously responded to posaconazole) and naïve patients, the clinical response rates were 88% and 81% respectively.

The MAH noted that the clinical response rates in the literature were 80% for itraconazole, 83% for voriconazole and 64% for caspofungin, among HIV subjects with clinical failure of first-line treatment.

Secondary endpoints –mycological response

In study 330 a 36.5% mycological response rate were achieved after 4 weeks of posaconazole treatment.

In study 298, cultures at the end of acute treatment were available only in 57% of subjects in the MITT population. At the end of the acute treatment period, 18% of these subjects were mycological responders – however, this analysis is not helpful because mycological cultures were not mandated for subjects considered to be clinical responders.

Secondary endpoints – relapse after cessation of treatment

In study 298, most patients were not assessed for clinical relapse at the end of acute treatment because they either went immediately into maintenance or discontinued study during acute treatment. More data are available for study 330, for relapse in the 4-week post-treatment period. This was defined as the presence of greater than 20 CFU/mL of the same *Candida* species at a post-treatment follow-up visit as was present at baseline. Of the 132 subjects (MITT subset) who were treatment responders at week 4 and who did not enrol into study 298 to continue treatment, clinical relapse rates were given as 28.8%, 4 weeks after the cessation of treatment.

3.4 Discussion on Clinical Efficacy

Azole susceptible oropharyngeal candidiasis

Two pivotal controlled clinical studies (209 and 331) were included in this submission for the 100mg dose of posaconazole for the azole susceptible oropharyngeal candidiasis indication. For both studies, the primary analysis used a non-inferiority margin of 15% whereas the CPMP/EWP/558/95 note for guidance on evaluation of new anti-bacterial medicinal products suggests a non-inferiority margin of 10% might be preferred.

Study 331 is the main study in patients with azole-susceptible oropharyngeal candidiasis. This was a randomised, active comparator study with evaluator blinding. This study was preceded by the dose-ranging study 209. Between these 2 studies, there were 260 patients (MITT subset) treated with the proposed 100 mg daily dose of posaconazole suspension, and 243 patients available for comparison receiving fluconazole suspension.

The initial major objection with the proposed indication in azole-susceptible oropharyngeal candidiasis was that it was worded in very broad terms, appearing to encompass 1st line use in all patients. This was not clinically justified, and was not supported by the submitted studies. The MAH agreed to restrict the indication to (in adults):

> *"Oropharyngeal candidiasis: As first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor"*

This wording is considered to be adequately supported by the submitted data. In particular, the extrapolation from HIV infected patients to immunocompromised patients generally is accepted by the CHMP. The amended SPC also makes clear that use in these patients should be by a physician experienced in the management of fungal infections, as with the other indications for posaconazole.

Study 331 was *designed* as essentially an open study, whilst evaluation of clinical response was carried out by a blinded person. Given this, the MAH was asked to comment on a number of possible sources of bias in this study which might have arisen from the open-label design. It was noted that, despite the limitations raised for this endpoint, *non-inferiority was shown* for the objective measure of mycological response for the pre-defined non-inferiority margin, and borderline met using a stricter 10% non-inferiority margin. Taking into account that the clinical relapse results are reasonably compelling in this study, this point has been addressed satisfactorily. The inclusion and exclusion criteria, choice and assessment of endpoints were acceptable in study 331, and the 2 treatment groups were well balanced. The duration of the treatment period and the length of follow-up were reasonable.

The dose-ranging study 209 provides some limited justification for the dose regimen of posaconazole used, although a very clear dose-response was not shown in this study. As an additional caveat, the dose-ranging study compared a posaconazole capsule to a fluconazole capsule, whilst the subsequent *study 331* compared posaconazole suspension to fluconazole suspension. The relative bioavailability between the research capsule and oral suspension was not formally evaluated. The MAH noted that a *post hoc* evaluation of the cumulative data set comprising bioavailability data for the capsule, tablet and suspension formulations estimated that the point estimate of the suspension to capsule (AUC and C_{max}) would be approximately 109.7% and 96.9%, respectively, using a comparison of the geometric means. It should be noted that a suspension would achieve greater local concentrations in the oropharynx than a capsule, and it is not clear that any increase in efficacy going from capsule to suspension would be the same for both posaconazole and fluconazole.

In the study 209, the subjects were treated with POS 400 mg BID for 1 day, followed by 100 mg QD for 13 days, compared with the subjects received FLU 200 mg QD for 1 day, followed by 100 mg QD for 13 days. The clinical success rate (cure or improvement) achieved with 100 mg (87%) was equivalent to that achieved with FLU 100 mg (85%). There is no separate *posology* for patients who cannot take food. The MAH has given a reasonable justification that the three-times daily regimen proposed, in comparison to the twice-daily regimen in the current indications, maximises exposure in such patients. The MAH made a number of additional clarifications to the SPC regarding the posology, and regarding advice for patients with diarrhoea or other gastrointestinal disease.

Turning to the choice of *comparator*, the dose of fluconazole in study 331 was 200 mg on day 1, followed by 100 mg QD on days 2-14. The usual dose given in the UK national SPC for fluconazole is 50 mg once daily for 7 - 14 days, which may be increased to 100 mg daily "In unusually difficult cases of mucosal candidal infections". This would certainly include HIV patients, as used in this study, and recurrent cases. A number of the references submitted refer to use of fluconazole at 100-200 mg per day for oropharyngeal candidiasis. Although not mentioned in the Diflucan SPC, a 200 mg fluconazole loading dose on the 1st day will enable optimum plasma levels to be reached quickly, and makes for a fairer comparison with the posaconazole dose schedule used. The patients in study 331 would have been difficult to treat. Certainly they had a significant degree of immunosuppression, with mean CD4 count below 100 cells/mm^3, and overall the dose of fluconazole comparator chosen is considered acceptable.

The *primary efficacy* variable in the two azole-susceptible OPC studies was the clinical success rate (defined as cure or improvement) after 14 days of treatment in the Modified Intent-to-Treat (MITT) subset.

The results of study 331 showed that in azole-susceptible patients with oropharyngeal candidiasis, 14 days of posaconazole therapy was *non-inferior* to the comparator fluconazole regimen for the primary endpoint, clinical success rate, at the end of the treatment period. In the primary MITT subset the percentages of patients with cure or improvement after 14 days of treatment were 91.7% in the Posaconazole group and 92.5% in the fluconazole group. The majority of subjects in each group were assessed as cured at this timepoint. This was consistent with the effect of this dose regimen in the dose-ranging study. As well as coming within the margins pre-specified in the protocol, posaconazole therapy was non-inferior using a margin of 10%. The Note for Guidance document (CPMP/EWP/558/95) suggests that this margin might be preferred, although an even tighter margin might be considered in light of the relatively high response rates found on fluconazole. The MAH's

assumption as to what the upper limit of the difference (5.04%) might represent in terms of potential loss of chance for patients is accepted by the CHMP. There is a suggestion that posaconazole would retain a significant part of the effect, and that the potential loss of efficacy would be minimal enough to be considered not clinically relevant.

Secondary endpoints suggest that the clinical and mycological response rates 4 weeks after the end of treatment favour the posaconazole group. Further analyses of the mycological responses endpoint were requested in order to interpret this. The response rates for both treatments were presented by the MAH for the mycological endpoint using the MITT and per protocol populations for those patients who had a positive culture for *Candida* species at baseline, and these results were similar to the MITT population. The clinical response rates 4 weeks after the cessation of treatment were similar between POS and FLU; however, subjects treated with POS had a significantly greater sustained mycological success rate 4 weeks following cessation of treatment than subjects treated with FLU (40.6%, versus 26.4%, respectively; P=0.0376). This suggests that over a longer observation period more of the subjects treated with FLU than POS might go on to clinical relapse. The MAH has however noted the lack of strong correlation between clinical and mycological responses in OPC, and the greater relevance of clinical response to patient care.

The primary endpoint results for study 331 were consistent in the protocol evaluable subset, and were supported by the secondary endpoints including measures of mycological response. The results in the comparator arm were in line with expectations.

All the above-discussed results suggest that POS was at least *as effective as fluconazole* in the treatment of HIV subjects with azole-susceptible OPC. In addition, POS is associated with fewer mycological relapses off therapy.

Azole refractory oropharyngeal and/or oesophageal candidiasis

For these claimed indications there were submitted two clinical studies, 330 and 298, which were both open-label and uncontrolled. The MAH failed to justify the lack of a comparator arm. In addition no formal historical comparison with a control group has been carried out, and no adequate justification has been given for the dose of posaconazole studied.

In the study 298 the number of patients with a diagnosis of oesophageal candidiasis has not even been specified and the mycological response is quite low: only 18% of all MITT subjects were mycological responders at the end of the acute treatment period. There is neither mention of local antifungal treatment permitted during the study nor of antiprotease administration

Besides, a 3-month evaluation is rather unusual and late; it is usually done at 3 weeks. This long period of evaluation should involve the follow-up of CD4 count and the mention of antiretroviral treatment given as any patient immunity improvement could impact positively on the clinical response. This study did not allow supporting the claimed indication in the treatment of azole refractory oropharyngeal and/or oesophageal candidiasis.

In the study 330, the open-label design as well as the small sample size (n=22) of this study did not allow CHMP to draw any conclusion from its results.

The Azole refractory oropharyngeal and/or oesophageal candidiasis indications were fully discussed in the preliminary assessment of this application. As the CHMP could not conclude on a positive Benefit/Risk balance in these indications the MAH withdrew both these proposed indications.

4 Clinical Safety

The pooled data is divided into two groups, based on the differences in the study designs, posaconazole doses administered and populations studied:

- **Controlled oropharyngeal candidiasis (OPC):** pooled data from the randomised, blinded, active-controlled trials in non-refractory OPC in subjects with HIV disease (studies 209 and 331); posaconazole administered up to 400 mg/day in comparison with fluconazole 100 mg/day for 14 days.

- **Refractory oropharyngeal candidiasis (OPC):** pooled non-comparative data from trials in oropharyngeal and/or esophageal candidiasis refractory to standard courses of therapy with azole antifungals (fluconazole or itraconazole) in subjects with HIV disease (study 330 and 298); posaconazole administered up to 800 mg/day for up to 15 months.

The higher proportions of patients presenting Treatment-Emergent Adverse Events (TEAEs) in the refractory Oropharyngeal Candidiasis pool compared with the controlled OPC pool may reflect the severity of illness in the refractory population as evidenced by the lower CD_4 counts in these patients and the resultant complications of advanced HIV disease (e.g. a greater number of subjects with respiratory symptoms in the refractory group)

No age-related comparison could be made, as nearly all subjects were 18-65 years of age (only 1 patient >65 years in each group). The safety profile appeared similar when considered by race; however the number of patients is limited in some groups.

Deaths
In the controlled OPC pool, the proportions of patients who died were similar with POS (3 %) and FLU (2 %). Most of the deaths were attributed to progression or complications of underlying HIV disease.
In the refractory OPC pool, 22 % of patients died. Most of these deaths were attributed to AEs considered unlikely related to POS or to progression or complications of underlying HIV disease. One death was attributed to the complications related to OPC.

Two deaths were considered by the investigator to be possibly related to POS.

Serious adverse events (SAEs)
For the OPC pool, the SAEs for study 209 are presented separately from the SAE summaries for the rest of the pool because of the unique data handling used for this study. SAEs reported for at least 2 % of patients in either treatment group included Fever, Anaemia, Diarrhoea, Pneumonia, Dehydration, Disease Progression, Sepsis.

SAEs were reported for 13 % of patients on POS and 18 % of patients on FLU. The most commonly reported SAE was fever (3 % with POS; 6 % with FLU).

For the remainder of the OPC pool, the SAEs reported for at least 4 % of patients in any group were fever, neutropenia, AIDS, pneumonia, Dehydration, Diarrhoea, Vomiting, Candidiasis Oral, Coughing, Nausea, Sepsis.

The proportions of patients with SAEs were similar for the two treatment groups (10 % with POS and 13 % with FLU). Respiratory insufficiency was reported for two POS-treated patients (1 %); all other SAEs each were reported in one POS-treated subject.

There were no treatment-related SAEs reported for patients treated with POS.

In the refractory OPC pool, SAEs were reported for 55 % of patients. The most commonly reported SAEs were fever (13 %) and neutropenia (10 %). Treatment-related SAEs were reported for 14 % of

patients. Neutropenia (5 %) and abdominal pain (2 %) were the only treatment-related SAEs reported for more than 1 % of patients on POS. Most subjects with treatment-related SAEs of neutropenia had a history of neutropenia and were taking many concomitant antiretroviral medications.

Treatment discontinuations
There were AEs that led to study-drug or study discontinuation or death in at least 2 % of patients in the OPC pool.

In the controlled OPC pool, 9% of patients on POS and 5% of patients on FLU had AEs that led to discontinuation or death. The difference between the two treatment pools resulted from a greater proportion of POS-treated patients with gastrointestinal system disorders (3 % with POS; 1% with FLU) and with AEs categorised as infections and infestations (3% with POS; 1% with FLU). No individual AEs that led to study discontinuation were reported for more than 1% of subjects with either treatment. The most commonly reported treatment-related AEs that led to study-drug or study discontinuation or death for patients on POS were fever, nausea, and rash, each reported for 1% of patients on POS and ≤1% of patients on FLU.

In the Refractory OPC pool, 34% of patients had AEs that led to study-drug, study discontinuation, or death. The most commonly reported of these AEs were AIDS (7%), respiratory insufficiency (3%), neutropenia, pneumonia, and sepsis (2% each). The most commonly reported treatment-related AEs that led to study-drug or study discontinuation or death were vomiting, cardiac failure, increased hepatic enzymes, neutropenia, rash, and thrombocytopenia, each reported for 1 % of patients.

The safety profile of POS in OPC is similar to that observed in refractory invasive fungal infection (rIFI) pool and in FLU arm. Most of the SAEs reported are expected taking into account the treated populations. Most patients presented confounding factors in the occurrence of SAEs such as underlying disease, progression of disease, multiple concomitant medications which may have contributed to the occurrence of SAEs, treatment discontinuation or death

Separately the safety data from the two bioequivalence/bioavailability studies have been reported and are presented below:

Safety – Studies P03409 and C90-180

No major concerns in terms of safety have been identified. The majority of the adverse events reported during these studies were considered to be unrelated to treatment. The incidence of adverse events was low, with no notable differences between the formulations. Most of the adverse events reported were mild to moderate in severity.

4.1 Risk Management Plan

The MAH provided a RMP proposal consisting of a safety specification Pharmacovigilance Plan and a 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 indications of oropharyngeal candidiasis and 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 to 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 signaling 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 MAH had undertaken the commitment to perform drug interaction studies 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 information included in the SPC, no further need for minimisation measures have been identified.

However a revised Risk Management Plan will be submitted as per the FUM of this opinion to include the safety concerns raised by the CHMP. In this revision hepatic events, hypokalaemia, worsening of depression, the thrombotic thrombocytopenic purpura (TTP) and pulmonary haemorrhage are included for close monitoring.

The postmarketing surveillance program consists of continual review of individual cases and periodic aggregate review of reports received and review of other sources including literature. The MAH will collect and analyze data in the form of case reports as part of routine pharmacovigilance. In particular, pulmonary events that could be reflective of pulmonary phospholipidosis will be considered during the individual and periodic aggregate review. Expedited reports will be submitted as part of routine pharmacovigilance.

The MAH will submit PSURs, which will focus on overall safety of posaconazole, primarily in the context of serious unlisted events, non-serious unlisted events in addition to anticipated adverse drug reactions associated with 'azoles' in general.

Signalling and trend analysis will consist of identification of potential safety signals to be further evaluated by the MAH pharmacovigilance physicians, and in the first year in analyses of available pharmacovigilance databases.

4.2 Discussion on the Clinical Safety

As seen in the randomised, controlled, first-line OPC studies (209 and 331), the POS safety profile was similar to that of FLU. No clinical difference was observed in the types of TEAEs or AEs leading to discontinuation when POS was compared to FLU in this patient population.

The bioavailability of posaconazole after oral administration appears to be affected by the quantity of food intake more than any demographic or disease factor. Therefore, to optimise exposure to obtain maximum therapeutic benefit, it was recommended to administer each dose with food containing fat content or a standard nutritional supplement. This is mentioned in the Summary of Product Characteristics. Unfortunately no related studies have been performed to exactly demonstrate the above relationship

In the OPC studies, the incidence of nausea, vomiting, diarrhea, and constipation was similar between the POS and FLU treatment groups. POS did not exhibit an increased incidence of cardiac adverse events, vision disorders, hepatic disorders and neurologic disorders which were previously reported for itraconazole or voriconazole. The proportion of subjects reporting AEs associated with hepatic dysfunction was similar in the POS and FLU treatment groups. Overall, the majority of hepatic associated AEs in this category were considered not to be related to study drug treatment.

Elevated liver function tests were reversible on discontinuation of therapy and in some instances these tests normalised without interruption of therapy. Therefore, it is prudent to recommend routine monitoring (particularly liver function tests and bilirubin) for patients who have abnormal liver function tests during POS therapy to screen for the development of more severe hepatic injury. Discontinuation of POS should be considered if clinical signs and symptoms are consistent with development of worsening liver disease.

POS should be used with caution in patients with severe hepatic impairment. In these patients, the prolonged elimination half-life may lead to increased exposure.

Following the discussion on the clinical safety the MAH commits to provide a revised Risk Management Plan including the close monitoring of hepatic events, hypokalaemia, worsening of depression, thrombotic thrombocytopenic purpura and pulmonary haemorrhage.

The overall safety profile is considered acceptable and in line with the data previously presented during the initial Marketing Authorisation application. The new concerns appearing during this assessment will be closely monitored by the MAH in the future as per the commitment.

5 Overall Conclusion and Benefit/Risk Assessment

Following the initial assessment the azole refractory oropharyngeal and/or oesophageal candidiasis indications were withdrawn by the applicant. Therefore, the Overall Conclusions and the Benefit/Risk Assessment presented here concern only the indication of azole-susceptible oropharyngeal Candidiasis.

To support this indication, two pivotal controlled clinical studies (209 and 331) were included in this submission for the 100mg dose of posaconazole for the azole susceptible oropharyngeal candidiasis indication. For both studies, the primary analysis used a non-inferiority margin of 15% whereas the CPMP/EWP/558/95 Note for Guidance on evaluation of new anti-bacterial medicinal products suggests a non-inferiority margin of 10% might be preferred. However the data assessed here support the indication of the Oropharyngeal Candidiasis. It was shown that the poasacozanole is considered *non-inferior* to fluaconazole in terms of *primary efficacy*.

The *posology* of this indication has been assessed and proposed for the immunocompromised population. The MAH has suggested a once a day of 200 mg loading dosage following of 100 mg posaconazole daily administration for the next 13 days regarding the indication under examination. Also although there are no specific studies assessing the interaction with food, it was recommended that posaconazole is administered with high fat food and/or in special cases with a food supplement depending on the state of the patients. All the above suggestions have been accepted by the CHMP.

The *Safety* profile has been assessed following the data submitted for the clinical studies performed. Although the safety profile was not dramatically changed, the MAH has committed to submit a revised Risk Management Plan to closely monitor the hepatic events, hypokalaemia, worsening of depression, thrombotic thrombocytopenic purpura and pulmonary haemorrhage adverse reactions in the future and post-marketing, together with the submission of PSURs and Annual Safety Reports.

In conclusion the CHMP considered that the relevant points have been adequately addressed and it recommends the granting of the Marketing Authorisation for the indication of Oropharyngeal Candidiasis.

Benefit/Risk assessment

As regards efficacy, posaconazole has been shown as non-inferior to the comparator fluoconazole for the indication of azole-susceptible oropharyngeal candidiasis.

The safety profile of the studies was considered as acceptable and the commitment of the MAH to submit a revised Risk Management Plan was taking into account. The commitment includes the mentioning of hepatic events, hypokalaemia, worsening of depression, thrombotic thrombocytopenic purpura and pulmonary haemorrhage in the new Risk Management Plan (RMP) as safety concerns, and to submit a revised RMP

Therefore taken into account the clinical data presented during the efficacy and safety assessment, it is considered that the *benefit/risk ratio* for the proposed indication in azole-susceptible oropharyngeal candidiasis is positive.

Recommendation

Based on the CHMP review of data on efficacy and safety the CHMP considered by consensus that the benefit/risk ratio of Noxafil was favourable for the indication of azole-susceptible oropharyngeal Candidiasis and therefore recommended the proposed changes in the Summary of Product Characteristics and the Package Leaflet.

6 Changes To The Product Information

Product Information

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 data submitted did not support the broad indication in oropharyngeal candidiasis (OPC) or the treatment of refractory oropharyngeal (rOPC) and/or oesophageal candidiasis (rEC). However, a revised wording was proposed by the MAH and accepted by the CHMP following the assessment of this variation which does not include the treatment of refractory oropharyngeal (rOPC) and/or oesophageal candidiasis (rEC). Consequently sections have been revised so the finally agreed indication is as:

Section 4.1 "Therapeutic indication"

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

(…)

"- Oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor".

The following sections of the Summary of the Product Characteristics have also been updated.

The Section 4.2 "Posology and method of administration" was updated to reflect the assessment discussion and to incorporate the dose adjustments related to the specific indication and the state of the patients.

The *Section 4.4 "Special warnings and special precautions for use"* was updated to incorporate the findings from the assessment of Safety and to highlight the precautions for the use of posaconazole in patients with serious underlying medical conditions (e.g. hematologic malignancy).

Due to the state of the patients receiving posaconazole the *Section 4.5 "Interaction with other medicinal products and other forms of interactions",* was revised especially for the patients receiving cyclosporine, and in consequence now includes the safety data assessed.

The *Section 4.8 "Undesirable effects*", has been reworked and presented in a way to better reflect the safety assessment in the new indication.

The *Section 5.1 "Pharmacodynamic properties"* and the *Section 5.2 "Pharmacokinetic properties"* have been updated to include the relevant clinical studies and the results that have been presented in support of this indication.