20 February 2014
EMA/159150/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Noxafil

International non-proprietary name: POSACONAZOLE

Procedure No. EMEA/H/C/000610/X/0028

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme Limited submitted on 07 March 2013 an extension application for Marketing Authorisation to the European Medicines Agency (EMEA) for Noxafil 100 mg gastro-resistant tablet, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 intend d) of the Commission Regulation (EC) No 1234/2008.

Merck Sharp & Dohme Limited is already the Marketing Authorisation Holder for Noxafil 40 mg/ml oral suspension (EU/1/05/320/001).

The applicant applied for the following indication: Noxafil is indicated for use in the treatment of the following 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.

The legal basis for this application refers to:

The application submitted is composed of administrative information, complete quality data, and a clinical bioequivalent study.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) [P/0289/2012] on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP [P/0289/2012] was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant did not seek scientific advice from the CHMP.

Licensing status

Noxafil has been given a Marketing Authorisation in European Union since 25 October 2005.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Schering-Plough Labo N.V.

Industriepark 30, Zone A

BE-2220 Heist-op-den-Berg

Belgium

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Dr. R. Suvarna

- The application was received by the EMA on 07 March 2013.
- The procedure started on 27 March 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2013.
- During the PRAC meeting on 14 July 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 22-25 July 2013, the CHMP agreed on the consolidated List of Questions

to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 July 2013.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 October 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 November 2013.
- During the PRAC meeting on 05 December 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the CHMP meeting on 16-19 December 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 January 2014.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 04 February 2014.
- During the meeting on 17-20 February 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Noxafil 100 mg gastro-resistant tablet

2. Scientific discussion

2.1. Introduction

Posaconazole is a broad spectrum triazole antifungal indicated in the systemic treatment of pathogenic yeasts and moulds and is currently available as an oral suspension (Noxafil). The oral suspension is administered 3-4 times daily and must be taken with food (preferably a high fat meal) to ensure adequate systemic exposure.

The applicant has sought to maximise systemic absorption and reduce the food effect by developing an acid resistant tablet (gastro resistant tablet). The product incorporates a pH sensitive polymer (hypromellose acetate succinate) which limits dissolution in the stomach, thereby maximising dissolution and absorption in the small intestine.

2.2. Quality aspects

2.2.1. Introduction

The product is presented as new gastro resistant tablets containing 100 mg of posaconazole as active substance.

Other ingredients are: hypromellose acetate succinate, cellulose microcrystalline, hyprolose, silica dental type, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, macrogol, titanium dioxide (E171), talc, iron oxide yellow (E172).

The product is available in a PVC/ polychlorotrifluoroethylene laminate blister with push-through aluminium lidding.

2.2.2. Active Substance

The active substance used in the proposed gastro resistant tablets, pocasonazole, is the same active substance as that approved for the currently authorised oral solution.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the development was to obtain a solid tablet of a size that was easy to swallow and that provided sufficient solubility of the active substance in the intestinal environment to enhance bioavailability and reduce the food effect and absorption variability observed with the authorised oral suspension.

The new pharmaceutical form is manufactured with the currently approved active substance which is also used for the other already authorised oral solution.

All the chosen excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The focus of the commercial formulation development was to develop a formulation that met the proposed Quality Target Product Profile (QTPP) exhibited the desired in-vitro, in-vivo performance, showed good stability and was easy to process. Early formulation design focussed on the prior knowledge gained from development of an oral suspension and established that the tablet should deliver low solubility in the stomach (low pH) and high solubility in the small intestine (neutral pH). A delayed release gastro-resistant film-coated tablet, which comprises a solid dispersion of the active substance in Hypromellose Acetate Succinate (HPMCAS) was developed. HPMCAS is a pH sensitive polymer stabiliser excipient which was selected to form a solid dispersion using a hot melt extrusion (HME) method. The pH sensitive solubility of the HPMCAS limits posaconazole release at low pH (pH<4). At neutral pH (pH6.8), the high solubility of HPMCAS allows posaconazole to be released. Three prototype formulations were developed to optimise the excipient quantities and compared to a capsule containing only the extrudate (no excipients).

The applicant has utilised a Quality by Design approach to finished product development, which has been generally adequately conducted. Manufacturing process development used Design of Experiments to establish Proven Acceptable Ranges (PARs) for manufacturing process parameters. The development data provided adequately support the proposed reduced in process testing of tablet crushing strength and tablet weight during compression (critical step).

The primary packaging consists in a PVC/Aclar laminate blister with push-through aluminium lidding. The finished product manufacturer tests the primary packaging for identification (IR), visual examination and overall thickness. Acceptance criteria was presented and considered acceptable. A declaration was also provided showing that the materials in the primary packaging are compliant with Directive 2002/72/EC and Directive 94/62/EEC.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process consists of 6 main steps: premix and blending, hot melt extrusion, milling, blending and lubrication, compression and film coating. The process is considered to be a standard manufacturing process.

The applicant has satisfactorily demonstrated through development using Quality by design (QbD) principles, that the manufacturing process is adequately controlled within the PARs specified. The proposed in process controls for tablet crushing strength and tablet weight are therefore considered appropriate and are satisfactorily underpinned by risk assessment

The manufacturing process is generally well described and process validation will be conducted on the first three commercial scale batches of the finished product. An acceptable validation protocol has been provided.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC, UV), assay (HPLC), degradation products (HPLC), dissolution (HPLC) and uniformity of dosage units (Ph Eur).

Batch analysis results are provided for a seven batches (development and commercial scale) confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three batches of finished product representative for the commercial scale stored under long term conditions for 12 months at 25ºC / 60% RH, for up 12 months under intermediate conditions at 30°C/75%RH and for up to 6 months under accelerated conditions at 40ºC / 75% RH according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay (HPLC), degradation products (HPLC), and dissolution (HPLC). The analytical procedures used are stability indicating. Additional data were also provided for moisture content and polymorphic form.

In addition, photostability studies were conducted in accordance with ICH Q1B using one batch and data provided. The samples were analysed for description, assay, impurities, moisture content and dissolution. No significant changes were observed thus demonstrating the proposed container closure system adequately protects the tablets from light.

Based on available stability data, the shelf-life and as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of this new pharmaceutical form Noxafil 100 mg gastro-resistant tablets has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

This application is supported by the non-clinical safety program conducted for the currently marketed POS oral suspension. No additional pharmacology or toxicology studies were conducted in support of the POS solid oral tablet. A pharmacokinetic (PK) study in non-human primates (NHP) was conducted with various oral and intravenous (I.V) formulations and data from this study was used to bridge the solid oral tablet formulation to the current marketed oral suspension. The proposed final clinical formulation was not used in this NHP study, however pH-sensitive polymer (hypromellose acetate succinate, HPMCAS was used in this NHP study.

2.3.2. Pharmacology

Not applicable.

2.3.3. Pharmacokinetics

A pharmacokinetic (PK) study in non-human primates (NHP) was conducted with various oral and intravenous (I.V) formulations and data from this study was used to bridge the solid oral tablet formulation to the current marketed oral suspension (Tablet A, Tablet B and capsule). The proposed final clinical formulation was not used in this NHP study, however pH-sensitive polymer (hypromellose acetate succinate, HPMCAS was used in this NHP study.

Male Cynomolgus monkeys were given single oral (60 mg) or I.V doses of either 0.4 ml/kg (1 mg/kg dose) and 2 ml/kg (5 mg/kg dose). Blood samples were taken pre-dose, 0.25, 0.5, 0.75, 1, 2, 4, 8, 24, 48, 72, 96 and 120 hours post-dose. The various formulations can be seen in the Table below.

Group	Formulation	Description	Batch No.	SCH 56592 Concentration	Excipients
1	Oral Suspension	Suspension	81713-111	40 mg/mL	Polysorbate 80, Xanthan Gum, Citric Buffer, Glycerol Anhydrous, Liquid Glucose, Cherry Flavor,Titanium Dioxide, and Water
2	Solid Dispersion (LF)[a]	Capsule	83471-106	60 mg/capsule	Blue gelatin capsule (size 0) and Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS) Type LF
3	Solid Dispersion (MF)[a]	Capsule	83471-107	60 mg/capsule	Blue gelatin capsule (size 0) and Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS) Type MF
4	Semi-solid	Capsule	83471-111	60 mg/capsule	Blue gelatin capsule (size 0) and Benzyl Alcohol, Cremophor® EL, and Pluronic® F68
5-6	Solution for Injection	Micellar Solution	83073-127	2.5 mg/mL[b]	Solutol® HS 15 and Ethanol

a: LF and MF represent two different polymer forms of HPMCAS characterized by differences in the weight percentage of acetyl and succinoyl substituents. This results in different dissolution profiles for the LF and MF polymers; aqueous solubility of HPMCAS-LF and HPMCAS-MF begin at pH ≥5.8 and pH ≥6.2, respectively.

b: The IV formulations were supplied pre-formulated at 7.5 mg/mL. This stock solution was diluted to a final concentration of 2.5 mg/mL with 5% dextrose solution and gently shaken to obtain a clear solution.

Mean (range) pharmacokinetic parameters of posaconazole following a single 60 mg oral administration of various formulations of posaconazole

Study	Formulation	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(tf)}$, (ng·hr/mL)	tf (hr)
DM27344 (34)	Suspension[a]	4 (NA)	261 (190-332)	4950 (3140-6890)	48 (NA)
	Capsule (semi-solid)[b]	4 (4-8)	531 (287-1060)	11400 (5360-18400)	60 (48-72)
	Capsule (HPMCAS LF)[c]	4 (NA)	1280 (979-1460)	29600 (22500-37300)	84 (72-96)
	Capsule (HPMCAS MF)[d]	4 (4-8)	1480 (1020-1840)	38400 (24100-51200)	84 (72-96)

a: Suspension = Marketed product

b: Capsule (semi-solid) = Blue gelatin capsule (size 0) containing posaconazole plus benzyl alcohol,Cremophor EL, and Pluronic F68.

c: Capsule (HPMCAS LF) = Blue gelatin capsule (size 0) containing posaconazole and hydroxypropylmethylcellulose acetate succinate (HPMCAS) type LF, solid dispersion, spraydried.

d: Capsule (HPMCAS MF) = Blue gelatin capsule (size 0) containing posaconazole and HPMCAS type MF,solid dispersion, spraydried.

The over-all conclusion of this study was that following a single 60 mg posaconazole oral administration, all three prototype capsule formulations (i.e. those formations that used HPMCAS-MF polymer) increased posaconazole exposure when compared to an oral suspension indicating an increase in oral bioavailability. The formulation containing the HPMCAS-MF polymer form displayed the greatest increase (~7-fold) in exposure.

2.3.4. Toxicology

Not applicable.

2.3.5. Ecotoxicity / environmental risk assessment

The recommended dose of the oral suspension formulation is 200 mg (5 ml) four times a day for the treatment of refractory invasive fungal infections and 200 mg (5 ml) three times a day for the prophylaxis of invasive fungal infections. For the tablet formulation of posaconazole, there is a recommended loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter. An assessment of the risk was performed for the oral suspension and no significant risk to the environment related to the use of posaconazole was anticipated.

The Phase I screening for persistence, bioaccumulation and toxicity (PBT) indicates that further evaluation of posaconazole is not warranted due to a log Kow < 4.5.

Based on the outcome of the Phase I environmental assessment, the predicted environmental concentration in surface water (PECSURFACEWATER) for the active ingredient, posaconazole was 4 µg/L, indicating that posaconazole may represent a risk to the environment following its prescribed usage in patients. Therefore a Phase II-Tier A environmental effects assessment and concomitant risk assessment was required.

The outcome of the Phase II Tier A Assessment comparing the Predicted No Effect Concentration (PNEC) and PEC ratios conclude that posaconazole does not present a risk to surface water, ground water, micro-organisms or to sediment-dwelling organisms. Posaconazole will not bioconcentrate and is not expected to pose a significant risk to the environment due to normal patient use. Thus, no

further action was necessary in this case and no special precautionary or safety measures need to be taken for the storage, labelling, administration, and disposal of posaconazole.

A risk assessment for sediment dwelling organisms was conducted and calculated to be 0.01. Since this value is less than 1, posaconazole was considered unlikely to represent a risk to sediment dwelling organisms.

In response to questions, the applicant provided further information on the environmental risk of the proposed product.

The applicant has conducted a risk assessment for sediment dwelling organisms which includes a refinement of the Fpen based on published epidemiological data. A refined Fpen of 0.031% was used. This estimate was considered to be the upper limit of the population potentially exposed because it assumes all patients with the above-mentioned diseases will take posaconazole. The resulting PECSW was 0.12 µg/L.

A PNEC for sediment (PNECSED) of 0.76 mg/kg 760 (µg/kg) was calculated. The PEC for sediment (PECSED) was calculated using the refined Fpen of 0.031%, the highest soil Koc value for posaconazole, and a refined PECSW of 0.0011 µg/L, estimated using SimpleTreat 3.1. For this assessment, PECSED was conservatively estimated to be 8.06 µg/kg (0.0081 mg/kg). The PEC/PNEC for sediment was determined by comparing the PECSED to the PNEC based on the midge test (PNECSED). The ratio calculated by the Applicant was:

$$\frac{760\ \mu g/kg}{8.06\ \mu g/kg} = 0.01$$

The applicant stated that since this ratio is less than 1, posaconazole was considered unlikely to represent a risk to sediment dwelling organisms.

However, a PEC sediment of 963 µg/kg (dry sediment) by Simple Treat has also been calculated. The value is based on a lower vapour pressure (no votalization) for injection applications. Nevertheless, no risk for sediment is expected although the risk quotient is slightly above 1 (1.3) because the tested concentration in the sediment organism test (76 mg/kg mean measured) was far above the water solubility and no effect was observed.

The half-life of the parent posaconazole in two river sediments was calculated to be 20.4 and 21.1 days. The half-lives of the two major transformation products in in two river sediments were calculated to be 38 and 106.7 (metabolite M2) and 358.1 and 108.1 (M3). The Applicant states that the metabolites (M2 and M3) could not be named according to chemical nomenclature as their definitive structures are unknown.

However, different half-lives for the fate of the major transformation products (elucidated structure) of posaconazole in water/sediment systems have been calculated. Nevertheless, all three transformation products show persistence in sediment with half-lives >120d. Posaconazole is therefore classified as being persistent. The identified three transformation products can be included in the summary of the main study results with the DT50 values as follows:

M1 (cannot be named): stable in sediment, persistent

M2 (cannot be named): 215.9 d (DE recalculated, SFO), persistent

M3 (cannot be named): 358.1 d, persistent

The Applicant has also provided the bioconcentration test report (Wildlife International, Ltd., Posaconazole: A bioconcentration test with the bluegill (Lepomis macrochirus), Final report, 16-Oct-2012 which was cited in the environmental risk assessment. The results of the submitted bioconcentration test report were considered plausible although the validation criteria for the study failed. The test concentrations in the test chambers varied more than ± 20%. The applicant stated that the variability in analytical results was due to the initial impacts of aeration of test solutions. Aeration during the study was considered necessary to maintain dissolved oxygen concentrations to keep the large number of fish alive which were required for tissue sampling during the course of the test.

2.3.6. Discussion on non-clinical aspects

The non-clinical data and discussion provided in this submission adequately support this line-extension.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data and discussion provided in this submission adequately support this line-extension.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Relevant pharmacokinetics data came from the following 5 studies in healthy volunteers and one patient study:

Study	Short Protocol Titles	Study Design	Dose Levels (mg)	Food and Formulation (fasted if not specified)	Number of Subjects Treated with Active Drug	PK parameters
P04975	PK & food effect study in healthy volunteers (SD)	XO (4-way, 2-part)	100	Tablet A Tablet B Capsule Oral Suspension (OS) (Fasted & fed)	16	Single dose Cmax, AUC0-∞, AUC0-last
P05637	PK study in healthy volunteers (SD and MD)	Parallel / fixed sequence	200, 400	200 BID 200 QD 400 QD Tablet C-green (MD without regard to food)	19	Single dose Cmax, AUC0-∞, AUC0-last and multiple dose AUC0-∞, Cavg and Cmax
P07691	Relative bioavailability study in healthy volunteers (SD)	XO	100	Tablet C-green Tablet D-yellow OS	23	Single dose Cmax, AUC0-∞, AUC0-last
P07764	DDI study with drugs impacting gastric pH or gastric motility in healthy volunteers (SD)	XO	400	Tablet D-green	21	Single dose Cmax, AUC0-∞, AUC0-last
P07783	Absolute bioavailability and MD PK study in healthy volunteers (SD and MD)	XO	300	Tablet D-yellow IV solution MD 300 QD with Tablet D-yellow (MD: breakfast one hour after drug intake)	13 SD 12 MD	Single dose Cmax, AUC0-∞, AUC0-last and multiple dose AUCτ, Cavg and Cmax
P05615	Dose finding and confirmation study in patients receiving prophylaxis (MD)	Fixed sequence	200, 300	Tablet C-green Tablet D-green (Without regard to food)	20 (200 mg); 210 (300 mg)	single dose Cmax, AUC0-last, multiple dose AUCτ, Cavg, Cmin, Cmax

Three clinical pharmacology studies were conducted to evaluate the relative and absolute bioavailability of posaconazole administered as different tablets and dosage forms and/or the effect of food on the pharmacokinetics of posaconazole. (**P04975, P07691, P07783**)

In addition, a food effect study was carried out in the clock stop period with tablet D (study P112).

Study P04975

Study P04975 was an open-label, partially randomized, 4-way crossover, 100-mg single-dose, 2-part study, in 16 patients designed to characterize posaconazole pharmacokinetics for a new capsule and 2 new prototypical tablet formulations (tablet A and B) relative to the marketed oral suspension (Noxafil) in 16 healthy volunteers under fasting and fed conditions.

Posaconazole PK parameters after single dose administration of different posaconazole formulations in fed versus fasted state

Pharmacokinetic Parameters	Fasted			Fed			Ratio (Fed/Fasted)	
	N	GM†	95 % CI	N	GM†	95 % CI	GMR	90 % CI
Oral Suspension								
$AUC_{0\text{-last}}$ † (ng.hr/mL)	16	2665.15	(1940.92, 3659.61)	15	8149.23	(6783.74, 9789.58)	3.06	(2.51, 3.73)
$AUC_{0\text{-}\infty}$ † (ng.hr/mL)	16	3021.37	(2268.98, 4023.25)	15	8438.14	(7053.09, 10095.17)	2.79	(2.35, 3.32)
C_{max} † (ng/mL)	16	71.40	(49.24, 103.54)	15	238.42	(197.53, 287.78)	3.34	(2.58, 4.32)
Tablet A								
$AUC_{0\text{-last}}$ † (ng.hr/mL)	16	11001.30	(9588.70, 12622.01)	15	11251.2	(9799.25, 12918.29)	1.02	(0.92, 1.13)
$AUC_{0\text{-}\infty}$ † (ng.hr/mL)	16	11295.02	(9857.29, 12942.46)	15	11504.9	(10048.97, 13171.92)	1.02	(0.92, 1.13)
C_{max} † (ng/mL)	16	372.34	(323.30, 428.83)	15	316.11	(273.48, 365.38)	0.85	(0.75, 0.96)
Tablet B								
$AUC_{0\text{-last}}$ † (ng.hr/mL)	16	10780.92	(9583.00, 12128.60)	15	11651.9	(10113.72, 13424.11)	1.08	(0.98, 1.19)
$AUC_{0\text{-}\infty}$ † (ng.hr/mL)	16	11046.72	(9838.34, 12403.51)	15	11967.7	(10380.51, 13797.75)	1.08	(0.98, 1.19)
C_{max} † (ng/mL)	16	349.76	(311.11, 393.21)	15	329.86	(279.56, 389.21)	0.94	(0.83, 1.07)
Capsule								
$AUC_{0\text{-last}}$ † (ng.hr/mL)	16	10380.62	(8536.28, 12623.46)	15	11496.2	(9386.21, 14080.67)	1.11	(0.99, 1.24)
$AUC_{0\text{-}\infty}$ † (ng.hr/mL)	16	10686.56	(8848.88, 12905.87)	15	11788.0	(9663.34, 14379.94)	1.10	(0.99, 1.23)
C_{max} † (ng/mL)	16	322.85	(257.88, 404.18)	15	310.27	(244.79, 393.25)	0.96	(0.83, 1.11)

† Geometric mean computed from least squares estimate from a linear mixed effect model performed on the natural-log transformed values.

- Exposures for the posaconazole tablet (Tablet A and B) and capsule formulations were not markedly affected by food. (Consistent with historic data, a high-fat meal increased the mean peak and total exposures 2.5- to 3-fold when posaconazole was administered as an oral suspension.)
- Under both fasted and fed conditions, both posaconazole tablet formulations (tablets A and B) and the capsule formulation showed similar peak and total exposures.
- Under fasted conditions, the tablet formulations (tablets A and B) and capsule formulation had less intersubject variability in peak and total exposures than the posaconazole oral suspension.

Study P07691

This six-sequence, randomized, open label, three-period, single site, single-dose study compared three formulations of posaconazole (*tablet D, tablet C and oral suspension*) in healthy subjects (18 to 65 years old) male and female subjects with a BMI between 18 and 30 kg/m2.

The study was designed to assess the relative bioavailability between the posaconazole tablet D with posaconazole tablet C (both 100mg, fasted), and posaconazole tablet D **fasted** with posaconazole oral suspension **(fed)**.

Relative bioavailability of posaconazole tablet D versus POS tablet C:

Following a single-dose administration of 100 mg each, the rate and extent of absorption of posaconazole tablet D in fasted state was slightly lower compared to posaconazole tablet C in the fasted state.

Arithmetic Mean (CV) of Plasma Pharmacokinetic Parameters of posaconazole following 100 mg Tablet C, Tablet D, and Oral suspension (P07691)

Parameter (Unit)	Tablet C (n=23)	Tablet D (n=22)	Oral suspension (n=23)
AUC0-last (ng•hr/mL)	9202 (31)	8327 (33)	8018 (32)
AUC0-∞ (ng•hr/mL)	9632 (31)	8786 (33)	8482 (31)
Cmax (ng/mL)	329 (33)	288 (40)	249 (25)
tmax[a] (hr)	4.00 (2-6)	5.00 (3-12)	5.00 (4-12)
t½ (hr)	26.6 (24)	27.0 (27)	26.2 (26)
CL/F (L/hr)	11.5 (35)	12.7 (37)	12.9 (31)
Vz/F (L)	427 (39)	467 (25)	468 (26)

Arithmetic mean and CV (coefficient of variation as percent) presented in parentheses, unless noted otherwise

[a] Median (minimum, maximum).

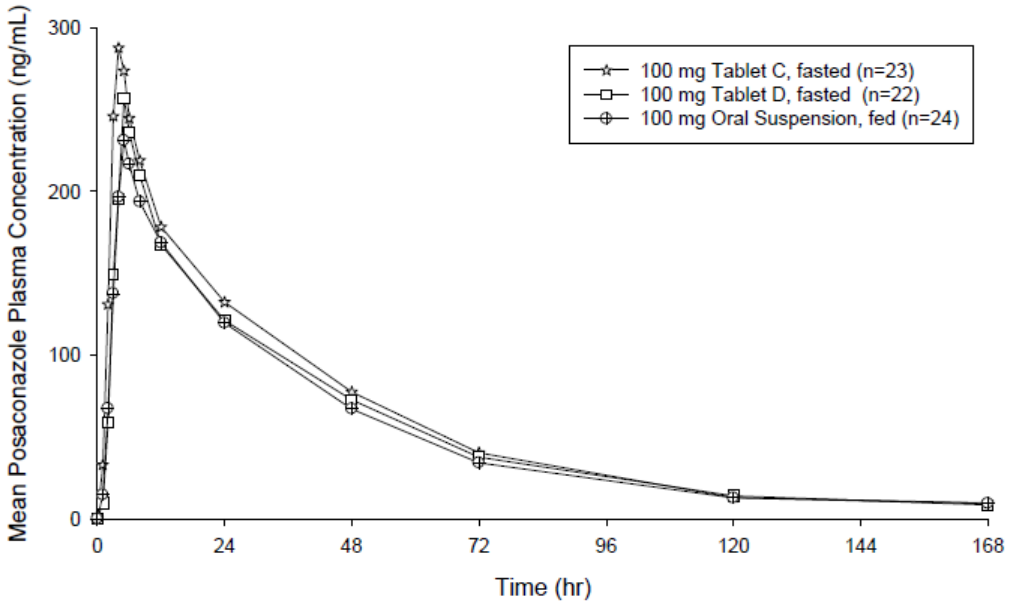
Relative Bioavailability of posaconazole Tablet D and posaconazole Tablet C (P07691).

		AUC 0-∞	AUC 0- last	Cmax
Ratio Tablet D / Tablet C	GMR	0.894	0.880	0.856
	90% CI	(0.821, 0.975)	(0.799, 0.970)	(0.748, 0.980)

Relative Bioavailability of posaconazole following Oral Administration of Tablet D and Oral Suspension (P07691).

		AUC0-∞ (hr*ng/mL)	AUC0-last (hr*ng/mL)	Cmax (ng/mL)
Oral Suspension, fed n=23	GM	8111.25	7625.72	241.59
	90% CI	(7295.69, 9017.98)	(6802.12, 8549.05)	(220.97, 264.14)
Tablet D fasted n=22	GM	8236.26	7723.3	265.28
	90% CI	(7253.45, 9352.23)	(6732.63, 8859.75)	(229.47, 306.68)
Ratio Tablet D / Oral suspension	GMR	1.015	1.013	1.098
	90% CI	(0.933, 1.105)	(0.920, 1.115)	(0.970, 1.243)

n: number of subjects, GM: (model based) geometric mean, CI: confidence interval; GMR: ratio of geometric mean



- Following a single dose administration of posaconazole 100 mg in the fasted state in healthy adults, the AUCs and Cmax of posaconazole tablet D were slightly lower compared to the AUCs and Cmax of posaconazole tablet C (10% and 14% lower respectively for AUC and Cmax);
- The differences in AUC and Cmax between the tablet formulation D and the oral solution are not clinically relevant.
- Following a single dose administration of posaconazole 100 mg in the fasted state for posaconazole tablet D and after a high fat meal for posaconazole oral suspension 100mg in healthy adults, the AUC and Cmax were considered to be similar between treatments.

Study P07783 (Part 1)

This study was an open label, two-part, single and multiple-dose study in healthy volunteer subjects. Part 1 of the study was designed to estimate the **absolute bioavailability of the FMI (posaconazole tablet D yellow)** compared to an investigational posaconazole intravenous (IV)

solution (via peripheral infusion) following a single dose administration of 300 mg for both formulations.

Part 2 of the study was designed to estimate the steady state pharmacokinetics (PK) of posaconazole tablet D following 8 days of daily administration of 300 mg and is described later.

Mean AUC0-last and AUC0-∞ for the posaconazole tablet (tablet D) (22722 and 23647 hr*ng/mL, respectively) were approximately 2-fold smaller compared to the posaconazole IV solution (42905 and 44380 hr*ng/mL, respectively). The mean maximum plasma concentration (Cmax) following the posaconazole tablet administration was approximately 7- fold lower than Cmax after posaconazole IV solution administration. Cmax was reached at a median of 5 hours for the tablet and at the end of infusion (0.5 hours) for the IV solution. The variability in Cmax and AUCs was consistently higher following posaconazole tablet administration (CV 38% to 48%, respectively) than following posaconazole IV solution administration (CV 19% to 32%, respectively).

The mean elimination half-life was similar (between 28 and 29 hours) for the two formulations. The (apparent) clearance and apparent volume of distribution were both approximately twice as high for the posaconazole tablet than for the posaconazole IV solution.

Summary of Posaconazole Pharmacokinetic Parameters by Treatment, presented as mean (%CV) (P07783, Part I).

Parameter (unit)	POS 3x100 mg tablet D [a] N = 13	POS IV solution 300 mg [b] N = 13
Cmax (ng/mL)	613.8 (37.9)	4257.7 (19.1)
tmax (hr)[c]	5 (3-6)	0.5 (0.25-0.5)
t½ (hr)	28.1 (25.6)	28.8 (27.8)
AUC0-last (hr*ng/mL)	22721.9 (46)	42904.7 (30.7)
AUC0-∞ (hr*ng/mL)	23647.3 (47.8)	44380.4 (32.2)
CL (CL/F) (L/hr)[d]	15.44 (45.8)	7.61 (41.4)
Vz (Vz/F) (L)[e]	583.33 (36.0)	294.64 (24.8)

[a]Treatment A; [b]Treatment B;
[c]median (min – max);
[d]CL = Clearance: CL/F=Apparent clearance following oral administration;
[e]Vz = Volume of distribution during terminal phase;
[e]Vz/F = Apparent volume of distribution during terminal phase.

Statistical Assessment of Formulation Effect on the PK Profile of Posaconazole (Pharmacokinetic Population)

	300 mg MK-5592, IV solution[a] N=13***		300 mg POS Tablet D[b] N=13***		Ratio (A/B)		Pseudo Within
PK Parameter	GM[c]	90 % CI	GM	90 % CI	GMR[d]	90 % CI	Subject %CV
AUC0-∞ (hr*ng/mL)*	41942.45	(35096.46, 50123.83)	21450.06	(17042.41, 26997.66)	0.511	(0.427, 0.612)	25.53
AUC0-last (hr*ng/mL)*	40648.00	(34174.18, 48348.18)	20665.59	(16402.51, 26036.66)	0.508	(0.423, 0.611)	25.98
Cmax (ng/mL)*	4175.99	(3735.51, 4668.40)	571.51	(467.11, 699.24)	0.137	(0.112, 0.168)	28.94
tmax (hr)**	0.50	0.25, 0.50	5.00	2.98, 6.00	-	-	-

[a]Treatment B; [b] Treatment A

[c]GM=Geometric mean; [d]GMR=Geometric mean ratio

* Back transformed least squares means and confidence interval (CI) from mixed effects model performed on natural log-transformed values.

** Median; minimum, maximum.

*** N denotes the number of subjects used in the mixed effect model.

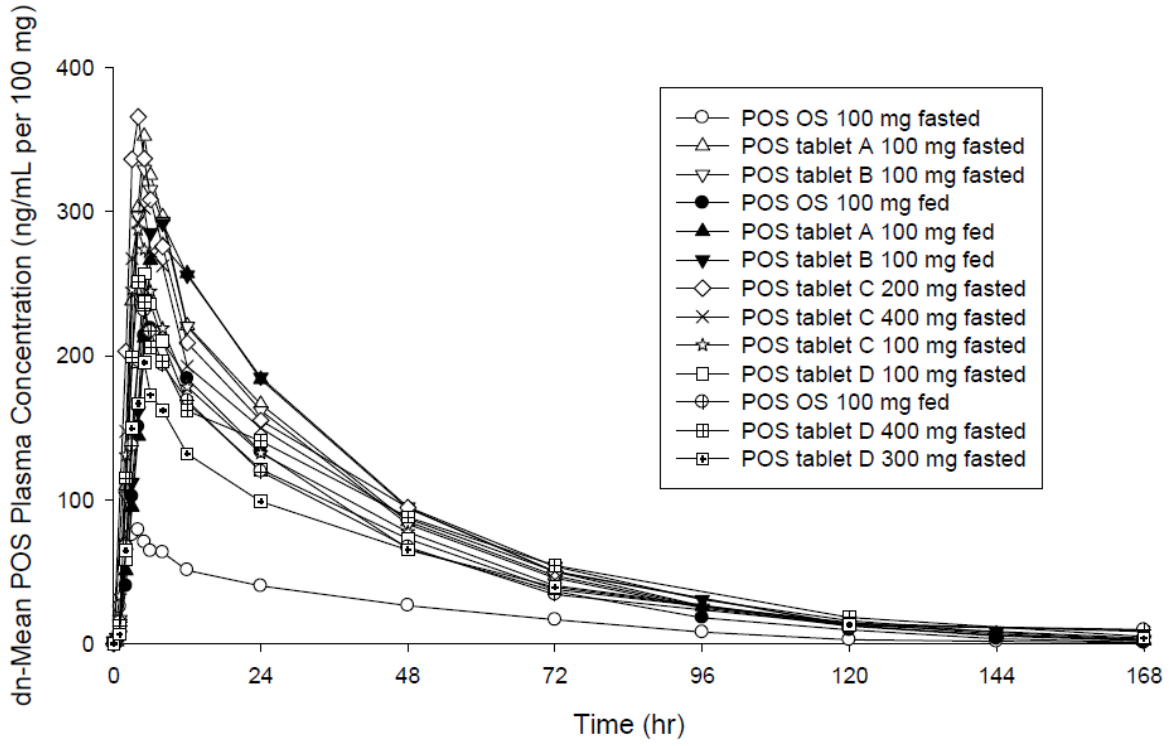
- Mean absolute bioavailability for tablet D was 0.54 (%CV 31.9%). Geometric mean absolute bioavailability was 0.51 (GeoCV 36.5%).

- Posaconazole mean AUC0-last and AUC0-∞ were approximately 2-fold smaller after posaconazole tablet administration compared to the IV reference. Posaconazole mean Cmax was approximately 7-fold smaller. Mean elimination half-life was similar between both formulations.

- ***Comparison and Analyses of Results Across Studies (Single dose data)***

For the direct comparison of bioavailability between the different tablet formulations, 2 studies (P07691 and P04975) were used. Results from other studies (P05637, P07764, P07783) were also included for comparison

Comparison of the Single-Dose (Dose Normalized to 100 mg) Concentration-Time Profile for the Posaconazole tablet and oral suspension (OS, oral suspension; fed; administered with high fat meal)



The figure illustrates that all formulations show similar Tmax values and terminal half-lives, although there is some variability between and within formulations.

Summary of the Mean (%CV) Results of the Comparative Bioavailability Studies of Posaconazole (100 mg) tablets (fasted) and oral suspension (fasted and fed).

Study No.	Dosage Form	Cmax (ng/mL)	tmax[a] (hr)	AUC0-last (hr.ng/mL)	AUC0-∞ (hr.ng/mL)	t½ (hr)
P04975	Tablet A (fasted)	385 (28)	5 (3-6)	11400 (26)	11700 (26)	26.1 (28)
	Tablet B (fasted)	358 (23)	5 (2-8)	11000 (22)	11300 (22)	25.0 (25)
	Capsule (fasted)	335 (27)	5 (4-8)	10700 (26)	11000 (25)	25.1 (27)
	Oral suspension (fasted)	84 (62)	4 (2-8)	2970 (50)	3420 (44)	29.2 (31)
	Oral suspension (fed)	243 (18)	6 (5-12)	8470 (25)	8750 (24)	25.1 (35)
P07691	Tablet D (fasted)	288 (40)	5 (3-12)	8327 (34)	8786 (33)	27.0 (27)
	Oral suspension (fed)	249 (25)	5 (4-12)	8018 (32)	8482 (31)	26.2 (26)

a: Median (range).

Comparison of PK Parameters for different formulations of Posaconazole Tablets across all studies- single dose administration

Study, formulation and dose	Cmax (ng/mL)		AUC0-last (hr*ng/mL)		t½ (hr)	
P04975[a]: 100-mg						
	Fasted	Fed	Fasted	Fed	Fasted	Fed
Tablet A	385 (28)	327 (23)	11400 (26)	11700 (24)	26.1(28)	23.7 (21)
Tablet B	358 (23)	348 (32)	11000 (22)	12100 (25)	25.0 (25)	25.3 (24)
P05637:, 200-mg [b]						
Tablet C	778 (29)		23000 (23)		25.1 (20)	
P05637:, 400-mg [b]						
Tablet C	1290 (29)		42800 (35)		26.1 (22)	
P07691, 100 mg[c]						
Tablet C	329 (33)		9202 (31)		26.6 (24)	
Tablet D	288 (40)		8327 (34)		27.0 (27)	
P07783, 300 mg[d]						
Tablet D	614 (38)		22722 (46)		28.1 (26)	
P07764, 400 mg[e]						
Tablet D	1090 (43)		40967 (47)		27.3 (37)	

Coefficient of variation (%CV) listed in parentheses.

a – P04975. The evaluation of the POS pharmacokinetics for Capsule, Tablet A, and Tablet B relative to marketed POS Oral Suspension in healthy volunteers. 100-mg (n = 16 for fasted and n = 15 for Fed)

b – P05637. The rising single and multiple doses of POS tablet C in dose selection and tolerability study. All PK parameters were taken on the first dosing day (Day 1), after a 10 hour fasting period. n = 10 for 200 mg and n =9 for 400 mg

c P07691. A relative bioavailability study to compare the pharmacokinetics of two different solid oral POS tablet formulations and POS oral suspension in healthy adults; n = 22/23

d: P07783 A parallel group, pharmacokinetic trial to estimate the absolute bioavailability and the multiple dose pharmacokinetics of POS tablets (tablet D-yellow)in healthy adults; : n = 13

e: P07764 ; A study to evaluate the effect of concomitant medications that affect the gastric pH and gastric motility on the pharmacokinetics of POS after POS tablet administration in healthy volunteers; n = 21

- after single dose administration, the dose normalized exposure of posaconazole Tablet C (in study P05637) was comparable to the exposure of 100 mg Capsule, Tablet A, or Tablet B in the previous study of P04975 (e.g.: AUC of 11400 hr*ng/mL with 100 mg Single Dose Tablet A under fasted condition).
- t1/2 values for Tablet C, Tablet A and Tablet B were comparable.
- the PK characteristics of Tablet C are similar to those of Tablet A or Tablet B

Study P112

A Relative Bioavailability Study to Assess the Effect of Food on the Posaconazole (MK-5592) pharmacokinetics Following the Administration of a Delayed Release Tablet in Healthy Subjects.

This recently completed study investigated the effect of a high fat meal on posaconazole exposure (300 mg, administered as 3 X 100 mg posaconazole, FMI, tablet D), following single dose

administration, in a cross-over design. The wash-out between successive dose administrations was at least one week. A total of 18 healthy male and female adult volunteers between 18 and 65 years (inclusive), BMI between 18 and 30 kg/m2 (inclusive), were enrolled. Blood samples for PK evaluation were collected pre-dose (0 hour) and up to 72 hours post dose on Day 1.

Results of this study show that when a single dose of 300 mg posaconazole Tablet D is taken with a high fat meal, posaconazole exposure in terms of AUC0-last and Cmax increased 51% and 16%, respectively.

Table 3-1. Statistical Comparison of Plasma Pharmacokinetics Posaconazole (MK-5592) Following Single Oral Dose Administration of 300 mg POS Tablet D (as 3 Tablets, each at 100 mg) to Healthy Subjects under Fasting and Fed Conditions

Pharmacokinetic Parameter	Treatment A Fasting Conditions		Treatment B Fed Conditions		Fed/Fasting	Pseudo Within-Subject %CV[c]
	N[a]	GM (95% CI)	N[b]	GM (95% CI)	GMR (90% CI)	
C_{max}[d] (ng/mL)	14[f]	893 (731, 1090)	16[g]	1040 (915, 1180)	1.16 (0.96, 1.41)	29.4
$AUC_{0\text{-}last}$[d] (hr·ng/mL)	14[f]	25600 (21500, 30400)	16[g]	38700 (35000, 42700)	1.51 (1.33, 1.72)	17.2
T_{max}[e] (hr)	14[f]	5.00 (3.00, 8.00)	16[g]	6.00 (5.00, 24.00)		

[a] Subject 003 voluntarily withdrew from the study during study period 2 (missing Treatment A).
[b] Subject 010 was withdrawn from the study during study period 2 (missing Treatment B) due to failed urine drug screen.
[c] Pseudo Within-Subject %CV = $100 * (\sqrt{(\hat{\sigma}_A^2 + \hat{\sigma}_B^2 - 2\hat{\sigma}_{AB}) / 2})$, where $\hat{\sigma}_A^2$ and $\hat{\sigma}_B^2$ are the estimated variances on the log scale for the two treatment groups, and $\hat{\sigma}_{AB}^2$ is the corresponding estimated covariance, each obtained from the linear mixed effects model;.
[d] Back-transformed least squares mean and confidence interval from ANOVA model performed on natural log-transformed values.
[e] Median (Min, Max) reported for T_{max}.
[f] N=14; Subjects 011, 012 and 016 had pre-dose values (Treatment A) for that period which were higher than 5% of their C_{max} and were excluded.
[g] N=16; Subject 002 had pre-dose value (Treatment B) for that period which was higher than 5% of their C_{max} and was excluded.
GM=Geometric least-squares mean; GMR=Geometric least-squares mean ratio; CI=Confidence interval;

Multidose studies with oral formulations

Study P05637 (tablet C)

This study was a randomized (3:1), third-party blind, placebo-controlled, single and rising multiple-dose study, designed to determine the multiple dose (primary objective) and single dose (secondary objective) pharmacokinetics of posaconazole for a new solid oral tablet formulation in healthy subjects. *Tablet C* was used in this study.

This healthy volunteer study (n= 24, from 18- 65 years of age) was performed to characterize the pharmacokinetics, safety and tolerability of *single and multiple doses* of posaconazole tablets and to evaluate the safety and tolerability. In addition, the effect of a twice daily (BID) loading dose and BID multiple dosing on the pharmacokinetics and safety was investigated.

A total of 24 subjects were to be randomized to one of two cohorts of 12 subjects each (9 active and 3 placebo) to receive single and multiple doses of posaconazole oral tablet.

For **Cohort 1 (n= 12)**, on Day 1, subjects received a single 200 mg dose of posaconazole or placebo. On Day 6, subjects received a 200 mg BID dose of posaconazole or placebo in the morning and

evening. On Days 7 through 14, subjects received a 200 mg once daily (QD) dose of posaconazole or placebo. On Days 15 through 22, subjects received 200 mg BID doses of posaconazole or placebo in the morning and evening.

For **Cohort 2**, on Day 1 subjects received a single 400 mg dose of posaconazole or placebo in the morning. On Day 6, subjects received a 400 mg BID dose of posaconazole or placebo in the morning and evening. On Days 7 through 14, subjects received a 400 mg QD dose of posaconazole or placebo. Cohort 2 did not contain the BID doses on Days 15 through 22 that were administered in Cohort 1. PK modelling data suggested that safe exposure limits would be exceeded at 400 mg BID.

Pharmacokinetic Results (Single Dose)

Table 3 Mean (%CV) of Posaconazole PK Parameter Following Single Oral Tablet Administration of Posaconazole 200 mg or 400 mg

Cohort	Dose (mg)	Day	n	Cmax (ng/mL)	Tmax[a] (hr)	AUCτ[b] (hr*ng /mL)	AUC0-last (hr*ng /mL)	AUC0-∞ (hr*ng /mL)	CL/F (L/hr)	t1/2 (hr)
1	200 QD	1	10	778 (29)	4.0 (3-8)	10500 (23)	23000 (23)	24000 (23)	8.80 (26)	25.1 (20)
2	400 QD	1	9	1290 (29)	5.0 (3-8)	18900 (34)	42800 (35)	46600 (35)[c]	9.55 (34)[c]	26.1 (22)[c]

CV = coefficient of variation expressed as a percentage (%CV); n = number of subjects; Cmax = maximum observed concentration; Tmax = time of maximum observed concentration; AUC0-last = area under the concentration-time curve from time 0 to the time of the final quantifiable sample; AUC0-∞ = area under the concentration-time curve from time 0 to infinity; CL /F = Apparent total body clearance; t½ = terminal phase half-life.

a: Median (range).

b: tau=24 hr

c: n=8; PK parameters for 1 subject could not be determined.

Following single oral administration of posaconazole tablet, the exposure increased in a dose-related manner. Based on log-transformed data, the dose-normalized Cmax and AUC for posaconazole 400 mg were 83% and 91% of that observed with the 200 mg dose).

Pharmacokinetic Results (Multiple Doses)

Following multiple oral administration of posaconazole tablet (200 mg QD, 200 mg BID, and 400 mg QD) for 8 days, the exposure among treatment groups increased in a dose-related manner. Based on log-transformed data, the dose-normalized Cmax and AUC for posaconazole 400 mg were 76% and 81% of that observed with the 200 mg dose. The accumulation ratios upon multiple doses were 3.14, 4.75 and 3.16 for 200 mg QD, 200 mg BID and 400 mg QD doses, respectively. The variability in exposure for 400 mg dose appeared to be relatively higher (CV% of 54% for AUC). The steady state appeared to be achieved by Day 13.

Mean (%CV) of Posaconazole PK with Multiple Oral Tablet C Administration of Posaconazole 200 mg QD, 200 mg BID, or 400 mg QD

Cohort	Dose (mg)	Day	n	Cmax (ng/mL)	Tmax[a] (hr)	AUCτ[b] (hr*ng/mL)	Cavg[c] (ng/mL)	t1/2 (hr)	R[d]
1	200 QD	6[e]	10	818 (26)[f]	5.0 (3-6)	6740 (21)	N/A		
		14	8	1800 (31)	5.0 (2-8)	31400 (32)	1310 (32)	NA	3.14 (24)
	200 BID	22	8	2980 (38)	4.0 (2-8)	30600 (38)	2550 (38)	31.4 (31)	4.75 (28)
2	400 QD	6[e]	9	1370 (36)[f]	5.0 (3-12)	11400 (35)	N/A		
		14	8	2940 (46)	5.0 (0-12)	56600 (54)	2360 (54)	26.6 (15)	3.16 (57)

CV = coefficient of variation expressed as a percentage (%CV); QD = once daily; BID = twice daily; n = number of subjects; Cmax = maximum observed concentration; Tmax = time of maximum observed concentration; AUCτ = area under the concentration-time curve over the dosing interval; Cavg = average concentration; t½ = terminal phase half-life; R = accumulation ratio.

a: Median (range).

b: tau=24 hr for QD and 12 hr for BID.

c: Cavg=AUC(tau)/tau.

d : Accumulation ratio is calculated as ratio of AUC(tau) of Day 14 to Day 1 (QD dosing) and Day 22 to Day 6 (BID dosing), respectively.

e: 200 mg BID and 400 mg BID loading dose on Day 6 for Cohort 1 and 2, respectively.

f: Pre-dose concentrations accounted for 1-5% and 1-9% of Cmax for 200 BID and 400 BID, respectively.

For single dosing

- Posaconazole AUC increased in a dose related manner between 200 and 400 mg
- Maximum posaconazole exposure was obtained at a median of 4 hr and 5 hr for 200 mg and 400 mg, respectively; mean half-life was comparable for the two dose levels (25-26 hr).
- Variability ranged from 23% to 35% for AUCs.
- Dose normalized posaconazole exposure on Day 1 was consistent with that observed in a previous study of posaconazole solid oral formulation (P04975, AUC0-∞ of 11400 hr*ng/mL after a single oral dose of 100 mg tablet under fasting condition).

For multiple dosing

- Posaconazole exposure increased in a dose related manner; when the dose increased in a 1:2 ratio, exposure increased in 1:1.9 and 1:1.8 ratios for Day 1 and Day 14, respectively, based on AUC.
- Maximum posaconazole exposure was obtained at a median of 4 hours and 5 hours, respectively; mean half-life was between 27 hours for 400 mg QD dosing and 31 hours for the 200 mg BID regimen. Variability for the 400 mg QD was higher (54% on AUC) than for the other dose regimens (32-38%).
- Accumulation ratios for the QD dose regimens were comparable for 200 mg and 400 mg (around 3.15)

- Steady state was reached by Day 13 (i.e. at 8 days of QD dosing including BID dosing on Day 6)

Study P07783 (Part 2, Tablet D)

Part 2 of the study was designed to estimate the steady state pharmacokinetics (PK) of posaconazole tablet D following 8 days of daily administration of 300 mg. (Part 1 was discussed earlier).

Part 2: On Day 1 of Part 2, subjects received a morning and evening dose of 300 mg posaconazole tablet D (3 X 100mg tablets twice daily as a loading dose). In the morning of Days 2 through 8, subjects received a single dose of 300 mg posaconazole tablets D yellow (3 X 100mg tablets).

Twelve (12) healthy adult subjects were enrolled for Part 2 and 11 subjects completed this study part.

Summary of posaconazole PK Parameters following posaconazole Tablet Multiple Dose Administration Part 2 Pharmacokinetic Population) (Mean and CV%)

Parameter (unit)	Treatment C N = 11
Cmax,ss (ng/mL)	2763.64 (20.6)
tmax,ss (hr)	4 (3-6)
t1/2,ss (hr)	34.9 (39.6)
AUC 0-τ (hr*ng/mL)	51618.03 (25.4)
Ctrough (ng/mL)	1784.7 (28.5)
Cavg (ng/mL)	2150.75 (25.4)
Lambda z,ss (1/hr)	0.023 (39.8)
Vz/F,ss (L)	294.31 (29.5)
CL/F,ss (L/hr)	6.17 (25.6)

Treatment C: Multiple doses of 3x100 mg POS tablet D-yellow, twice daily on Day 1 and once daily on Days 2 to 8.

Ctrough = Concentration immediately prior to dosing;

Cavg = Cavg=AUC(tau)/tau.

Assessment of Time to Reach Steady State using Posaconazole Plasma Trough Concentrations:

Study Day Comparison	LS Mean For Pair-wise Difference	90% CI For Pair-wise Difference
(Day 7 + Day 8)/2 vs. Day 6	1.05	(0.93, 1.19)
Day 8 vs. Day 7	0.98	(0.92, 1.05)
Day 6*	1646.04	(1413.7, 1916.5)
Day 7*	1748.58	(1503.7, 2033.3)
Day 8*	1717.47	(1461.9, 2017.7)

Least squares (LS) means, Ratio of LS means, and 90% Confidence Interval (CI) for ratio were transformed back to the linear scale.

* LS means and 90% CI for Days 6, 7 and 8 are presented on the original scale of measurement.

Subject 204 was excluded from the analysis because they had AE diarrhea;

11 subjects were used in the analysis.

- Following multiple-dose administration of posaconazole tablet D, posaconazole steady state was reached by Day 6 of 300 mg daily doses.
- The mean Cmax,ss was 2764 ng/mL (CV%= 20.6%) and occurred at a median of 4 hours post-dose at steady state. Mean Cavg was 2151 ng/mL and the variability (CV%) was 25.4%. Mean AUC0-τ was 51618 hr*ng/mL and the variability (CV%) was 25.4%.
- Apparent clearance and apparent volume of distribution at steady state were 6.2 L/hr and 294 L, respectively. Mean elimination half-life of posaconazole was 35 hours.

Pharmacokinetic interaction study

Study P07764

This was a randomized, open-label, single center, five-way crossover, single dose healthy volunteer study requested by the FDA to investigate whether differences in absorption of posaconazole tablets were observed by increasing gastric pH and by changing the gastric and intestinal motility through pharmacological intervention with 4 drugs:

In this study Tablet D green was used. Twenty-one (21) subjects were enrolled and 20 subjects completed the study, with 1 subject withdrawing consent prematurely.

Antacid: A single 400 mg (100 mg x 4) dose of posaconazole tablets was dosed immediately after administration of 20 ml of Mylanta Ultimate Strength liquid under fasted condition.

Ranitidine: The H2 receptor antagonist ranitidine (Zantac tablets) was dosed at 150 mg BID orally on Day 1. A single 400 mg dose of posaconazole tablet was administered one hour after administration of the first ranitidine dose under a fasted condition.

Esomeprazole: The proton-pump inhibitor esomeprazole (Nexium) was dosed as 40 mg once in the morning QAM x 5 days (Days -4 to 1). Then on the fifth day (Day 1) esomeprazole was administered with a single 400 mg dose of posaconazole tablet under fasted condition.

Metoclopramide: The prokinetic agent metoclopramide (Reglan) was dosed at the highest recommended dose, 15 mg orally four times daily, during two days, starting on Day -1. On Day -1, metoclopramide doses were to be taken on an empty stomach 30 minutes before meals and at bedtime. In the morning of Day 1 metoclopramide was to be administered together with a single 400 mg dose of posaconazole tablet under fasted condition.

Summary of geometric mean ratios and 90 % confidence intervals (CI) of AUC0-last and Cmax for treatment (Trt) B (Mylanta), Trt C (Ranitidine, Trt D (Esomeprazole), or Trt E (metoclopramide) compared to Trt A (posaconazole tablet alone)

	Trt B†/A† n=21/20		Trt C†/A n=20/20		Trt D†/A n= 20/20		Trt E†/A n= 20/20	
Pharmacokinetic parameter[a]	GMR	90% CI	GMR	90% CI	GMR	90% CI	GMR	90% CI
AUC0-last	1.04	(0.90,1.20)	0.97	(0.84,1.12)	1.02	(0.88,1.17)	0.93	(0.80,1.07)
Cmax	1.06	(0.90,1.26)	1.04	(0.88,1.23)	1.05	(0.89,1.24)	0.86	(0.73,1.02)

[a]: Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values
†Treatment A: A single 400 mg of POS tablet
†Treatment B: A single 400 mg dose of POS tablet + 20 mL of Mylanta ultimate strength liquid
†Treatment C: A single 400 mg dose of POS tablet + morning dose of 150 mg ranitidine tablet BID
†Treatment D: Esomeprazole 40 mg once in the morning QAM x 5 days (Days -4 to 1) + a single 400 mg dose of POS tablet
†Treatment E: A single 400 mg dose of POS tablet + metoclopramide, 15 mg four times daily during 2 days (Day-1 and 1)

In conclusion, there is no clinically meaningful effect of gastric pH or gastric motility on the pharmacokinetics of posaconazole after co-administration of posaconazole with each of these drugs affecting the gastric pH or gastric motility.

2.4.3. Pharmacodynamics

Not applicable.

2.4.4. Discussion on clinical pharmacology

The aim of the development programme was to produce a formulation that would improve exposure and avoid the requirement for multiple dosing taken with a high fat meal, which was recognised to pose problems in the target population. The proposed new tablet formulation is designed to inhibit the release of the active ingredient until the drug reaches the small intestine, where the entire dose of solubilised posaconazole is to be released triggered by the higher pH, aiming to maximize systemic absorption. During the development of the acid resistant pH-sensitive tablet formulation of posaconazole, several prototype formulations were tested (tablets A, B, C, capsule). The tablet formulations differed in their excipients, but the ratio of the solid dispersion composition of HPMCAS was held constant in all tablets (and the capsule). Dissolution showed similar release characteristics for all tablets with complete dissolution of the posaconazole tablets within 60 minutes, using two-stage dissolution with pH change from 2 to 6.8 at 30 minutes, mimicking conditions of use with a transit from highly acidic to less acidic environment in the GI tract. Tablet D (yellow) was chosen as the FMI. D yellow and D green differ in the colour coating only and can be considered equivalent.

Study P07691 demonstrated that tablet D, when given fasted, has a similar overall exposure when compared with the currently marketed posaconazole oral suspension administered after a high fat

meal, when both are given at a dose of 100mg. It is noteworthy that the approved dose for the oral suspension as prophylaxis 200mg, given 3 times daily, while the proposed dose for the tablet formulation in this indication is 300mg once daily. Following the CHMP discussion, a study investigating the food effect of tablet D was performed during the clock stop period and demonstrated that a food effect is observed with tablet D, but is considerably less than with the oral suspension. After a high fat meal, AUC is increased by 50% with the tablet compared to the fasting state. The effect on Cmax is small (16% increase).

A single dose study comparing tablet D to a non- approved intravenous solution (currently under evaluation in another line extension procedure) demonstrated an absolute bioavailability of around 50% in the fasting state. Variability for AUC and Cmax was higher with the tablet formulation, indicating that absorption factors contribute to CV%. As expected apparent clearance and Vz were twice as high for the tablet. T1/2 was around 28h for both formulations after a single dose.

Of note, these single-dose studies were performed with a posaconazole dose of 100mg. The dose proposed for marketing is 300mg (3 tablets of 100 mg), making this the preferred choice of dose for comparative bioavailability studies for a drug with linear PK.

Multiple dose studies were conducted with tablets C and D. Steady state was reached on Day 6- 8 of multiple dosing. There is relevant accumulation with multiple dosing, which is higher than expected, with an accumulation ratio of around 3. Half- life after 400mg QD multiple dosing was 26 h, as seen after single dose administration. Exposure increased approximately linearly between doses of 100mg and 400 mg with tablets D and C. Dose linearity of doses up to 800mg had previously been demonstrated for the oral suspension. Relevant interactions with drugs affecting stomach pH and emptying were not observed.

2.4.5. Conclusions on clinical pharmacology

The goal of the development programme was to produce a formulation with a reduced food effect and increased absorption.

With the results of study P112, it was demonstrated that the food effect of tablet D was relevantly reduced when compared to the oral suspension, but not entirely abolished. Exposure increases by about 50% with a high fat meal with the tablet compared to 3- 4 fold with the oral suspension. The effect on Cmax is small for the tablet formulation. The effect of lighter meals on AUC is unknown.

At a single dose of 100mg, tablet D given when fasted produces similar exposures as 100mg oral suspension when given in the fed state.

Tablet D (fasted) was shown to have an absolute bioavailability of around 50% compared to an investigational intravenous solution, which is currently under regulatory review in a parallel line extension procedure.

Inter-study comparisons showed that after single doses with the tablet formulations, there is an approximately linear increase of exposure up to a dose of 400mg.

The half- life for the 4 tablets A- D was similar, ranging from around 26- 29 hours, resulting from an apparent clearance of around 11- 15 L/h and a high volume of distribution. Exposures ranged from around 1140- 8400 hr.ng/mL and were lowest for tablet D.

There is significant accumulation (accumulation factor around 3) which is greater than expected. This may at least in part be due to differences in food intake. Steady state is reached by Day 6-8. Apparent clearance decreases and half-life is longer with multiple dosing, and AUC and Cmax increase. These effects are not fully explained, but posaconazole may inhibit its own metabolism, thereby reducing clearance over time. In addition, changes in food intake over time may increase exposure. This effect would be expected to be less pronounced with the tablet formulation and absent with an intravenous formulation.

Overall, the pharmacokinetics of posaconazole tablets have been sufficiently characterised, although the reason for the extent of accumulation seen is not fully clarified.

2.5. Bridging strategy, pharmacokinetics in target population and clinical efficacy

2.5.1. Bridging Strategy

This clinical program for the posaconazole tablet has been designed to demonstrate comparable exposure and safety for the posaconazole tablet among the same patient populations for which the posaconazole oral suspension has already been approved. The primary intent of the pivotal clinical study in patients (P05615) was to fully characterize the pharmacokinetics (PK) and assess the safety of the posaconazole tablet in neutropenic subjects (AML and MDS) and in subjects who had undergone a HSCT and were under treatment for GVHD.

The MAH states that a clear dose-response relationship has been identified with higher exposures associated with a higher likelihood of clinical response. In general, efficacy for prophylaxis appeared to be greater in posaconazole-treated subjects than in control subjects when posaconazole exposures were in the second or higher quartiles. This effect was seen not only in the pivotal Phase 3 prophylaxis studies (P 01899 and C/I98- 316) but also in patients with aspergillosis enrolled in the refractory IFI study (P00041)

Posaconazole Oral Suspension Exposure Response Analysis In Key Clinical Treatment and Prophylaxis Trials.

		P00041[a] (Treatment of refractory aspergillosis)		P01899[b] (Prophylaxis in AML/MDS)		C98-316[b] (Prophylaxis in GVHD)	
		Range	Response (%)	Range	Response (%)	Range	Response (%)
POSACONAZOLE	Q1	55-277	24	90-322	45.3	22-557	55.6
	Q2	290-544	53	322-490	63.0	557-915	79.4
	Q3	550-861	53	490-734	53.7	915-1563	82.5
	Q4	877-2010	71	734-2200	72.2	1563-3650	82.5

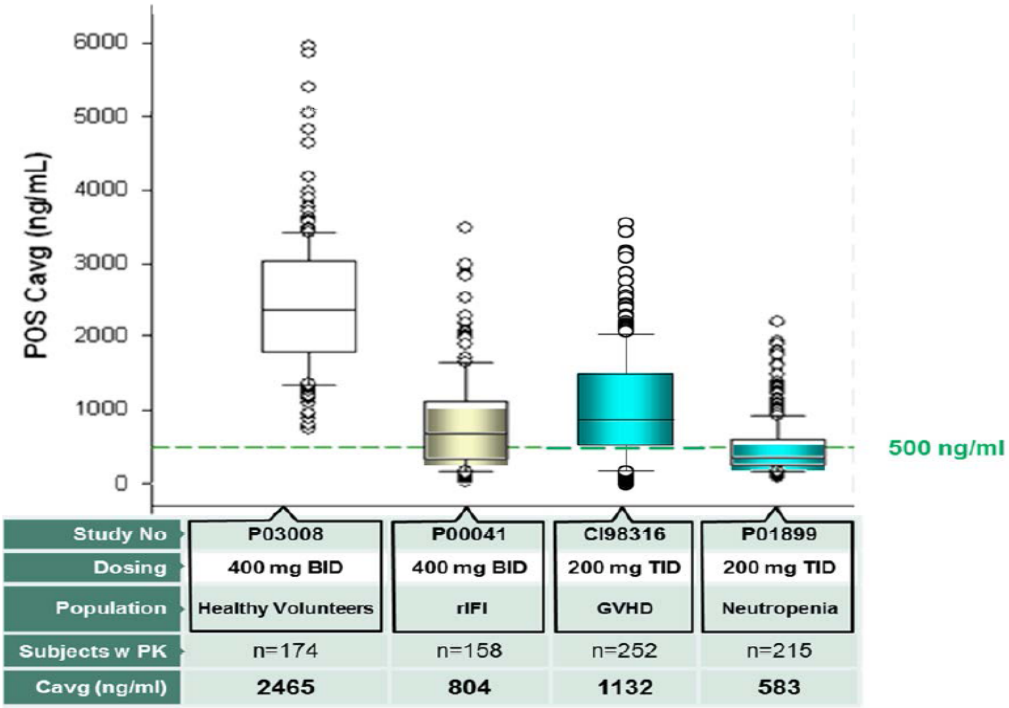
[a] Trial for salvage treatment of IFI
[b] Prophylaxis trial
AML=acute myelogenous leukemia, MDS=myelodysplastic syndromes, GVHD=graft versus host disease
Source data: [Ref. 5.4: 129, 249] and (CTD Section 2.7.3 [Sec. 2.7.3.4.1.1.1])

The plasma concentrations achieved in the 2 prior prophylaxis trials with posaconazole oral suspension at the approved clinical dose have been used by the MAH as a predictor of overall prophylaxis efficacy, and these 2 studies provide the basis for the target therapeutic exposure in the bridging study. In study P01899, the mean posaconazole plasma concentration following posaconazole oral suspension was 583 ng/mL, with 90% of patients attaining posaconazole average plasma levels (Cavg) greater than or equal to 228 ng/mL. In study C/I98-316, the mean posaconazole plasma concentration following posaconazole oral suspension was 1130 ng/mL with 90% attaining posaconazole plasma Cavg greater than or equal to 322 ng/mL.

Furthermore, a key fungal pathogen that is targeted with antifungal prophylaxis and antifungal treatment is *Aspergillus*. Based on in vitro data, the posaconazole minimum inhibitory concentration of 90% of isolates (MIC90) for *Aspergillus* species isolated from clinical infections is 0.5 ug/mL (500 ng/mL).

Hence, the exposure target for selecting a dose for the posaconazole tablet in the pivotal posaconazole tablet patient study (P05615) was a steady -state Cavg range between 500 ng/mL to 2500 ng/mL for 90% of subjects. This exposure range was selected based upon the exposure response relationship noted with posaconazole oral suspension in the prophylaxis of IFI setting (C/I98 -316 and P01899) as well as the studies that were conducted in the refractory IFI setting (P00041). It was expected that a greater proportion of subjects would attain Cavg greater than or equal to 500 ng/mL with the posaconazole tablet than with the oral suspension, as issues regarding limited absorption due to poor food intake were considered no longer relevant.

Figure 9-1 Summary of Observed POS Steady-State Exposures for POS Oral Suspension Healthy Volunteer and Key Patient Studies



Projected Exposure for POS Solution 200 mg QD and 300 mg QD=Box represents 25th to 75th percentiles, line inside the box represents median, whiskers represent 10th and 90th percentile, and points beyond whiskers represent outlier values (any subject with a value outside of the 10th and 90th percentile).

With regards to the upper exposure limit, the protocol P05615 specified that the upper limit exposure Cavg threshold for posaconazole tablet Phase 1B portion of the study was to be 3750 ng/mL. A similar study for the posaconazole IV solution (study P05520) specified an upper limit exposure Cavg threshold for the posaconazole IV study to be 3650 ng/mL. The maximum desired exposure target was related to safety based upon prior clinical and preclinical events with posaconazole. The development program for posaconazole tablet sought to maintain exposures within the upper limit of exposures achieved with previous posaconazole formulations. The highest posaconazole steady-state exposures in prophylaxis studies were noted in subjects with Graft Versus Host Disease (GVHD) receiving posaconazole prophylaxis (99th percentile of exposure: 3260 ng/mL). Posaconazole exposures in healthy volunteers receiving posaconazole oral suspension have been shown to be 2-fold to 3-fold higher than those found in patients and include exposures up to approximately 5960 ng/mL. Within this range of exposures, no dose-limiting safety events have been identified in either patients or healthy volunteers enrolled in posaconazole oral suspension clinical trials. In animals, preclinical findings of a possible association of an effect on steroidogenesis with high posaconazole exposure have been noted similar to that reported with other azoles. This effect has been observed in animals at an AUC of approximately 130,000 hr.ng/mL (Cavg of 5,400 ng/mL) with a no-effect level preclinically with AUC <90,000 hr•ng/mL (Cavg 3,750 ng/mL). Exposure was targeted to be within the range of posaconazole exposures previously studied and considered to be safe and effective in the prophylactic setting. The exposure target is based upon the range of exposures achieved, as well as the exposure-response relationship found in earlier controlled studies of posaconazole oral suspension.

- The exposure target range for the use of posaconazole tablets in patients in the prophylaxis setting was set as below:
  Cavg at steady-state levels ≥500 ng/mL or AUC ≥12,000 hr•ng/mL in at least 90% of subjects (per PK evaluable dosing cohort).
- Mean Cavg steady-state level ≤2,500 ng/mL or AUC ≤59,000 hr•ng/mL (per serial PK-evaluable dosing cohort)
- No subject with a mean steady-state plasma concentration >3,750 ng/mL or with a steady-state AUC >90,000 hr•ng/mL (per serial PK-evaluable dosing cohort)

Cavg was the exposure parameter used in studies with posaconazole oral suspension and therefore this was the major bridging PK parameter. In addition to the Cavg as the major bridging parameter, the Cmin is taken into account and evaluated against the Cavg requirements.

PK and exposure in target population: Main study (P05615)

This single pivotal Phase 1b/3 study was performed to evaluate the pharmacokinetics, safety, and tolerability of multiple dose administration of posaconazole tablet in patients receiving prophylaxis. Study P05615 was a single-arm, open-label, multicentre, global study of the pharmacokinetics and safety of posaconazole tablet used as prophylaxis in 230 adult subjects at high risk for IFIs.

Further details on the study design are given in section “Clinical efficacy” .

The primary objective of this study was the characterization the PK profile of posaconazole tablets in a representative subject population.

Treatment administered

Tablets were taken without regard to food. Planned treatment duration was up to 28 days, minimum duration 8 days

Population and sampling

Part 1 enrolled neutropenic subjects undergoing chemotherapy for acute myelogenous leukemia (AML) or myelodysplasia (MDS) with a minimum duration of therapy of 8 days and a maximum duration of 28 days.

Part 1A: 200 mg BID on Day 1, followed by 200 mg QD thereafter

Part 1B: 300 mg BID on Day 1, followed by 300 mg QD thereafter

The dose selection and decision to proceed to Part 2 were based on the posaconazole tablet exposure levels achieved and the safety observed among the Part 1 subjects.

Part 2 enrolled two patient populations. Neutropenic subjects undergoing chemotherapy for AML or MDS and subjects who were recipients of allogeneic hematopoietic stem cell transplant (HSCT). Patients received a dose of 300mg posaconazole per day (after a loading dose of 2x 300mg on day 1).

Sampling Part 1:

- Serial PK sampling on Day 1 and Day 8 at pre-dose, approximately 2, 4, 6, 8, 12 and 24 hours post-dose on Day 1 and Day 8 in all patients
- Trough levels on Day 2, Day 3, Day 8, Day 14, Day 21, and Day 28 (or EoT) in all patients

Sampling Part 2: Sparse PK sampling (trough, Cmin) in all subjects

- Serial PK sampling on Day 1 and Day 8 in a subset of ca. 30 HSCT patients

The primary PK parameter of interest was the plasma posaconazole exposures at steady state (Cavg). The desired exposure targets at steady state needed to be met in Part 1 to allow for dose selection for Part 2.

A dose was to be selected for Part 2 based on the following criteria in the serial PK-evaluable cohort:

- Cavg at steady-state levels ≥500 ng/mL or AUC ≥12,000 hr·ng/mL in at least 90% of subjects (per PK evaluable dosing cohort).
- Mean Cavg steady-state level ≤2,500 ng/mL or AUC ≤59,000 hr·ng/mL (per serial PK-evaluable dosing cohort)
- No subject with a mean steady-state plasma concentration >3,750 ng/mL or with a steady-state AUC >90,000 hr·ng/mL (per serial PK-evaluable dosing cohort)

In addition, Cmin values were to be evaluated similar to the Cavg.

PK Results

A total of 230 subjects were treated, 20 subjects treated with posaconazole tablet 200 mg (Part 1A), and 210 subjects treated with posaconazole tablet 300 mg (Part 1B, n=34; Part 2, n=176). The study treated 110 (48%) subjects with AML (new diagnosis), 20 (9%) subjects with AML (first relapse), 9 (4%) subjects with MDS, and 91 (40%) subjects with HSCT, as the primary diseases at study entry.

200 mg (Part 1A), Serial PK evaluable cohort

The predefined targets for dose selection for Part 2 were not achieved with the 200 mg dose. Six (6) of 18 subjects (33%) attained Cmin between 200 ng/mL and 500 ng/mL, and 12 of 18 (67%) attained Cmin between 500 ng/mL and 2500 ng/mL.

Arithmetic Mean (%CV) of PK Parameters in Serial PK-Evaluable Subjects Following Single and Multiple Dosing of Posaconazole Tablet (200 mg)

Dose = 200 mg									
Day	n	Cmax (ng/mL)	Tmax[a] (hr)	AUCtf (ng*hr/mL)	Cavg[b] (ng/mL)	Cmin (ng/mL)	C12hr (ng/mL)	CL/F (L/hr)	R[c]
1	18	652 (33)	4 (1.9-4.1)	4670 (33)	-	-	316 (30)	-	-
8	18	1310 (47)	4 (2.0-8.1)	23500 (49)	981 (48)	812 (55)	995 (46)	10.9 (53)	2.22 (59)

AUCtf=area under the concentration-time curve from time 0 to the time of the final quantifiable sample (12 hrs for Day 1, 24 hrs for Day 8); C12hr=observed plasma concentration at 12 hour post dose; Cavg=AUCtf/tf; CL/F=apparent total body clearance; Cmin=POS trough level immediately before a subject received the dose of POS on the day specified in the protocol; Cmax=observed maximum plasma concentration; CV=coefficient of variation, expressed as a percent (%); Day=study day on treatment; R=accumulation ratio based upon Cmax; tf=the time of the final quantifiable sample; Tmax=time of observed maximum plasma concentration; n= number of subjects.

[a] Median (minimum-maximum).

[b] Cavg=AUCtf/tf.

[c] R=Cmax Day 8/Cmax Day 1.

Note: Geometric mean (%CV) for Cmax, AUCtf, Cavg, and Cmin on Day 8 for 200 mg were 1180 (52) ng/mL, 20800 (56) hr.ng/mL, 869 (56) ng/mL, and 687 (70) ng/mL, respectively.

300 mg (Part 1b and Part 2), Serial PK evaluable cohort

45 of 50 (90%) subjects attained Cavg between 500 ng/mL and 2500 ng/mL, and 5 of 50 (10%) subjects attained Cavg between 2500 ng/mL and 3750 ng/mL. No subject's Cavg fell below 500 ng/mL or exceeded 3750 ng/mL.

The arithmetic mean Cavg at steady state was 1580 ng/mL and individual Cavg values ranged from 510 ng/mL to 3450 ng/mL. Overall, the pre-defined exposure targets required for dose selection were achieved at the 300 mg dose level.The variability in exposure (AUC) was approximately 40%.

Arithmetic Mean (%CV) of PK Parameters in Serial PK-Evaluable Subjects after Single and Multiple Dosing of Posaconazole Tablet (300 mg)

Dose = 300 mg										
Day	n	Disease	Cmax (ng/mL)	Tmax[a] (hr)	AUCtf (ng*hr/mL)	Cavg[b] (ng/mL)	Cmin (ng/mL)	C12hr (ng/mL)	CL/F (L/hr)	R[c]
1	50	AML/MDS + HSCT	908 (39)	4 (1.8-12.0)	6730 (40)	-	-	523 (50)	-	-
8	50	AML/MDS + HSCT	2090 (38)	4 (1.3-8.3)	37900 (42)	1580 (42)	1310 (50)	1550[d] (41)	9.39 (45)	2.51 (40)
1	17	HSCT	1030 (48)	6 (2.0-12.0)	7900 (49)	-	-	674 (54)	-	-
	33	AML/MDS	845 (29)	4 (1.8-8.1)	6130 (27)	-	-	445 (32)	-	-
8	17	HSCT	2390 (43)	4.1 (2.0-8.3)	44800 (45)	1870 (45)	1540 (49)	1900[e] (41)	8.11 (46)	2.69 (46)
	33	AML/MDS	1930 (32)	2.2 (1.3-8.1)	34300 (36)	1440 (36)	1190 (47)	1380 (35)	10.1 (43)	2.41 (35)

AML/MDS=acute myelogenous leukemia/ myelodysplastic syndromes; AUCtf=area under the concentration-time curve from time 0 to the time of the final quantifiable sample (12 hrs for Day 1, 24 hrs for Day 8) ; C12 hr=observed plasma concentration at 12 hour post dose; Cavg=AUCtf/tf; CL/F=apparent total body clearance; Cmin=POS trough level immediately before a subject received the dose of POS on the day specified in the protocol; Cmax=observed maximum plasma concentration; CV=coefficient of variation, expressed as a percent (%);Day=study day on treatment; GM=geometric mean; GM=geometric mean; HSCT=hematopoietic stem cell transplant; R=accumulation ratio based upon Cmax; Tmax=time of observed maximum plasma concentration; n = number of subjects

[a] Median (minimum-maximum).

[b] Cavg=AUCtf/tf.

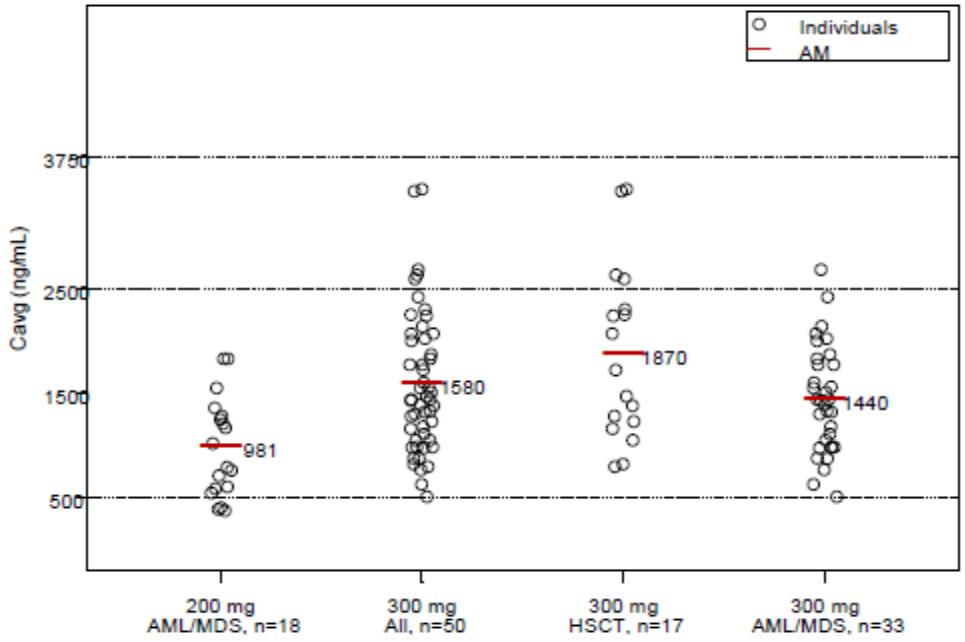
[c] R=Cmax Day 8/Cmax Day 1.

[d] n=49.

[e] n=16.

Note: GM (%CV) for Cmax, AUCtf, Cavg, and Cmin on Day 8 were 1950 (40) ng/mL, 34800 (44) hr.ng/mL, 1460 (44) ng/mL, and 1160 (56) ng/mL, respectively. For AML/MDS subjects, GM (%CV) for Cmax, AUCtf, Cavg, and Cmin on Day 8 for 300 mg were 1840 (35) ng/mL, 32100 (40) hr.ng/mL, 1340 (40) ng/mL, and 1066 (55) ng/mL, respectively. For HSCT subjects, GM (%CV) for Cmax, AUCtf, Cavg, and Cmin on Day 8 were 2180 (48) ng/mL, 40600 (49) hr.ng/mL, 1700 (49) ng/mL, and 1380 (52) ng/mL, respectively.

Individual Observed Posaconazole Cavg in Serial PK Evaluable Subjects Following 200 mg or 300 mg Multiple Dosing of Posaconazole Tablet



In Part 1 subjects, a strong correlation was found between the observed Cavg values and observed average Cmin values (R2=0.92). Using the serial PK data from both Parts 1 and 2, the following formula was developed to predict steady-state Cavg (predicted Cavg, pCavg) using observed Cavg and trough values (Cmin) on Day 8:

Predicted Cavg (pCavg) = 228 + 1.02 • Avg_Cmin.

Using this linear regression model the pCavg could be derived from the observed average Cmin values obtained at steady state in the Cmin PK-evaluable cohort. The average Cmin was calculated as the average of observed trough plasma values at steady state on Days 8, 14, 21 and Day 28/EOT:

Predicted Cavg (pCavg) Evaluation

Among 205 Cmin PK-evaluable subjects receiving 200 mg or 300 mg QD, the mean pCavg levels for 200 mg and 300 mg (1010 ng/mL and 1970 ng/mL) in the Cmin PK-evaluable cohort were higher than the observed Cavg values on Day 8 in the serial PK-evaluable subjects (981 ng/mL and 1580 ng/mL).

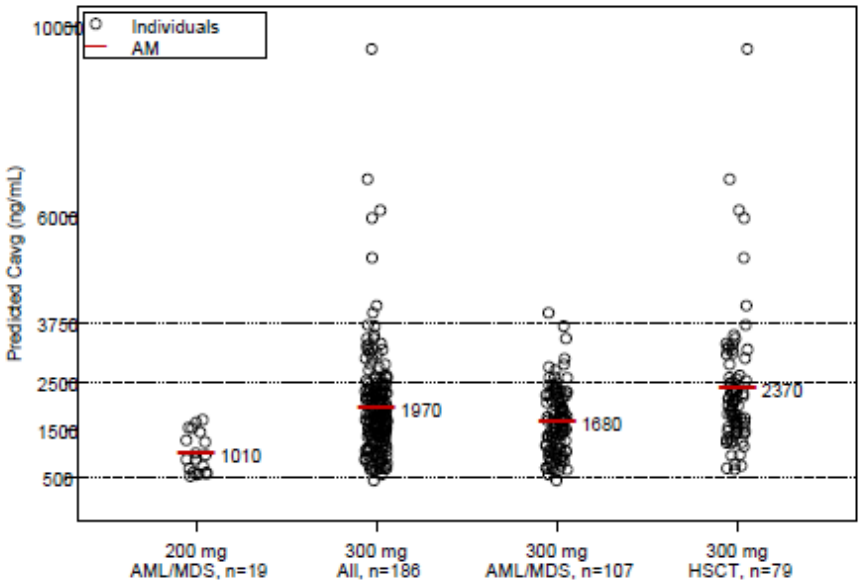
Arithmetic Mean (%CV) of Posaconazole Average Cmin and Predicted Cavg (pCavg) in Cmin PK Evaluable Subjects Following 200 mg or 300 mg Multiple Dosing of Posaconazole Table

Treatment	n	Disease	Average Cmin (ng/mL)		pCavg (ng/mL)	
			AM (%CV)	Range	AM (%CV)	Range
200 mg	19	AML/MDS	771 (53)	306-1470	1010 (41)	539-1720
300 mg	186	AML/MDS + HSCT	1720 (64)	210-9140	1970 (56)	442-9520
	107	AML/MDS	1430 (48)	210-3680	1680 (41)	442-3970
	79	HSCT	2110 (66)	445-9140	2370 (60)	680-9520

Frequency Distribution of Posaconazole Predicted Cavg (pCavg) in Cmin PK-Evaluable Subjects Following 300 mg Multiple Dosing of Posaconazole Tablet, Overall and by Underlying Disease

Dose = 300 mg			
	pCavg[a] (ng/mL)		
Disease State of Subjects	AML/MDS + HSCT	AML/MDS	HSCT
n	186	107	79
n (%) of subjects pCavg ≥200 ng/mL and <500 ng/mL	1 (0.5%)	1 (1%)	0
n (%) of subjects pCavg ≥500 ng/mL and <2500 ng/mL	151 (81%)	96 (90%)	55 (70%)
n (%) of subjects pCavg ≥2500 ng/mL and <3750 ng/mL	27 (15%)	9 (8%)	18 (23%)
n (%) of subjects pCavg ≥3750 ng/mL	7 (4%)	1 (1%)	6 (8%)

Plot of Individual Posaconazole pCavg in the Cmin PK-Evaluable cohort following 200 mg or 300 mg Multiple Dosing of Posaconazole Tablet



As expected from the correlation, the evaluation of the average Cmin showed similar results.

Exposure comparison for Posaconazole Tablets and Posaconazole Oral Suspension in Patients

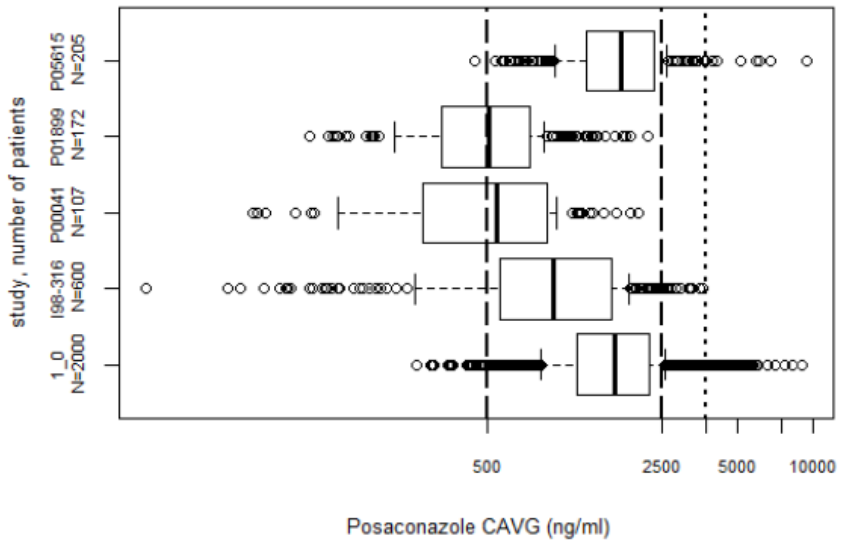
The steady state exposure after administration of 300 mg posaconazole tablet is higher than posaconazole oral suspension in all 3 studies.

Cavg Quartile Analyses of pivotal patient studies with Posaconazole tablet and Posaconazole oral suspension

	POS tablet		POS oral suspension		
	P05615 prophylaxis in AML and HSCT		CI98-316 Prophylaxis in GVHD	P01899 Prophylaxis in Neutropenia	P00041 Treatment - Aspergillosis
	200/300 mg QD (Day 1 200/300 mg BID)		200 mg TID	POS 200 mg TID	POS 200 mg QID (hospitalized) then 400 mg BID
Quartile	pCavg range	avg Cmin range	Cavg Range	Cavg Range	Cavg Range
Q1	442-1223	210-978	21.5 – 557	89.6 – 322	55 – 277
Q2	1240-1710	995-1456	557 – 915	322 – 490	290 – 544
Q3	1719-2291	1465-2028	915 – 1563	490 – 734	550 – 861
Q4	2304-9523	2040-9135	1563 - 3650	734 - 2200	877 – 2010

pCavg: predicted Cavg
[Ref: 5.3.5.2: P056151

Figure 10-7 Comparison of Posaconazole Cavg in the Previous Prophylaxis Trials (P01899 and C/I98-316) and Treatment Trial (P00041) Versus the POS Tablet Trial (P05615)



Black line in box is median, box depicts the 25th and 75th quantiles; the whiskers depict the 0.3 x inner quartile range (equivalent to 10th and 90th percentiles). Open dots represent individuals outside these 10 and 90th percentiles.

Table 9-6 Distribution of POS Exposures in Clinical Trials with the Oral Suspension and Tablet Formulations and the Percentage of Subjects Achieving the Exposure

Percentage of subjects achieving concentrations	POS Cavg (ng/mL)				
	Treatment of Refractory IFI P00041 Oral Suspension 400 mg BID N = 158	GVHD Prophylaxis C/I98-316 Oral Suspension 200 mg TID N = 252	AML Prophylaxis P01899 Oral Suspension 200 mg TID N = 215	P05615 Tablet 300 mg Dosing Cohort 300 mg QD N = 186	Healthy Volunteers Oral Suspension 400 mg BID N = 174
Maximum	3490	3650	2200	9523	5960
1%	2990	3264	1880	6786	5850
5%	2070	2476	1348	3693	3890
10%	1650	2092	1067	3197	3410
25%	1112	1563	734	2344	3040
50%	673	915	490	1785	2380
75%	332	557	322	1354	1790
90%	155	216	190	929	1350
95%	85.3	112	135	752	1210
99%	35	51	98	649	786
Minimum	18.7	21.5	89.65	442	745

Shaded Area = POS Tablet Exposure Target (500 ng/mL – 2,500 ng/mL) for 90% of subjects

Source Data: Posaconazole (SCH 56592) Intravenous Solution Briefing Document April 2010 and P05615.

Analysis performed across trials (pooled analyses and meta-analysis)

Composite pharmacokinetic analysis

The composite PK analysis included the 5 healthy volunteer studies (P04975, P05637, P07764, P07691, P07783) presented above and 1 patient study (P05615). The healthy volunteer studies included doses of 100 mg, 200 mg, and 400 mg for single dose data, and 200 mg and 400 mg for multiple dose (steady state) data. The patient study P05615 was analysed separately, with doses of 200 and 300 mg administered QD (following BID dosing on day 1).

The objective of this composite PK analysis is to evaluate the factors that affect single and multiple dose posaconazole pharmacokinetics in healthy subjects and to estimate intra-and inter individual variability. Additionally, factors affecting posaconazole PK in patients were evaluated.

All individual PK parameters were dose normalized to 100 mg and natural log transformed and evaluated in a linear mixed effects model including fixed effects of dose (since posaconazole PK is slightly less than proportional for doses higher than 300 mg), formulation, race, and gender, a random effect of subject within study, and covariates of age and weight.

Population PK (popPK) model

The primary objectives of the analysis were

- To develop a population PK model of posaconazole tablet using data in healthy volunteers and patients and quantify the variability of posaconazole exposure
- To perform covariate analysis to identify the demographic and clinical factors that might affect the exposure of posaconazole

- To conduct simulations to estimate the mean Cavg and Cmin and the percent of population with exposures above 500 ng/mL.

This population PK analysis includes the data from the 5 healthy volunteer studies (P04975, P05637, P07764, P07783 and P07764) and 1 patient study (P05615). Only data from healthy volunteers and patients who were treated with posaconazole tablet were included. Data from all tablet formulations were used (tablet A, B, C, and D) with posaconazole tablet D as the final formulation.

In total, 335 subjects (104 healthy volunteers and 231 patients (1 patient had one pre-dose sample and was thus not included in the PK analyses in the study) and 5756 observations were available for the analysis.

Results

The data were best described by a 1-compartmental model with a sequential zero first order absorption and a first order disposition from the central compartment. Model was parameterized in terms of clearance (CL) and volume of distribution (V).The inter-individual variability was assumed log normal and inter-occasion variability on the absorption and bioavailability parameters was incorporated. Data were log transformed for fitting purposes. The residual variability was described by two parameters, one for the (clinical) phase 1 and one for the (clinical) phase 2/3 data.

Covariate analysis showed 5 statistically significant covariates, 1 continuous (weight on F1) and 4 categorical (Regimen on Clearance, food on KA (absorption rate constant), formulation and subpopulation on F1 (bioavailability)

Model qualification showed that the model was adequate and robust and could be used for simulation purposes and calculation of the relevant exposure parameters (AUCô, Cavg, Cmin). Although the Cmax was underpredicted (more pronounced at single dose compared to multiple dose), the prediction of AUC0-τ and Cmin was good with in most cases a slight overprediction. The model best describes the PK of posaconazole in the patient population.

A food effect study has been recently conducted with the posaconazole 300 mg Tablet D after the initial submission. Hence, the original existing model has been updated by including the food effect data of P112.

Table 7c.1. Parameter estimates for the original and updated POPPK model

	Original POPPK model		updated POPPK model	
Parameter	**Estimate**	**RSE (%)**	**Estimate**	**RSE (%)**
Fixed effects				
CL (L/h)	9.70	5.00	9.69	5.16
V (L)	393	2.77	393	2.85
KA (1/h)	0.853	7.75	0.801	7.24
D1 (h)	2.54	3.45	2.66	3.29
COR Ka-D1	-0.586	15.2	-0.629	15.8
Weight on F1	-1.03	8.91	-1.01	10.2
Regimen on CL	0.750	5.87	0.751	5.85
Tablet A/B on F1	0.247	21.5	0.25	19.1
FED* on KA	0.530	17.3	0.452	12.8
AML/MDS on F1	-0.167	25.8	-0.166	26.4
FED* on F1			0.442	9.8
Non-Fixed effects				
IIV CL	37.9	13.1	37.3	12.7
IIV KA	57.5	29.3	52.2	32.5
IIV F1	24.2	26.7	23.6	26
IOV KA	71.1	17.0	71.1	16.5
IOV D1	48.6	9.83	48.2	10
IOV F1	21.4	23.3	20.9	23.2
Residual				
STDEV (Healthy volunteers)	0.42	8.69	0.422	7.92
STDEV (Patients)	0.322	10.3	0.322	10.3

CL: clearance; V: volume of distribution; KA: absorption rate constant; D1: duration of zero-order absorption into depot compartment; COR: correlation factor to account for high correlation between KA and D1; F1: bioavailability; IIV: interindividual variation: IOV: interoccasion variability; STDEV: standard deviation.
*FED on KA is effect on Tmax present in P112 and P04975; FED on F1 is only for P112.

Although food is now identified as a significant covariate on bioavailability in this updated popPK model, the table above shows that the estimates of all the other model parameters are quite similar in the updated popPK model relative to the original popPK model.

The MAH concluded that

- Posaconazole tablet pharmacokinetics can be modelled adequately with a 1- compartmental pharmacokinetic model with sequential zero/first order absorption.
- Moderate variability was estimated for bioavailability (24 and 21% respectively for between and within subject variability) and clearance (38%).
- Variability for the rate of absorption (Ka) was relatively high as there was limited data to support precise assessment of this parameter.

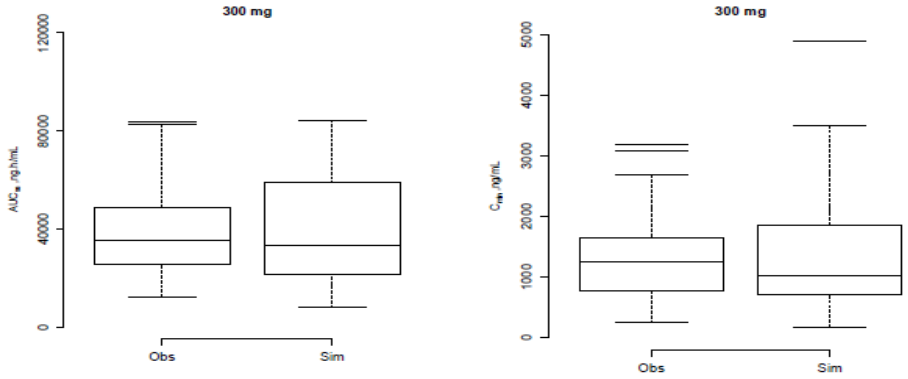
Model predicted exposures for posaconazole tablet formulation

The popPK model was developed from the available data on the tablet formulation. This open one compartmental population PK model with sequential zero/first order absorption model was subsequently used to simulate patient PK profiles and then model estimated AUC and Cmin were compared against observed values in order to evaluate the performance of the model for the target patient population. As indicated by the boxplot, the final PK model is able to simulate patient PK parameters comparable to the observed ones.

Table 7.1 Simulated Percentage of Subjects with POS Exposures (Cmin and Cavg) below 500 ng/mL and above 3750 ng/mL, and Cavg between 500 and 2500 ng/mL, 2500 and 3750 ng/mL for Doses of 200, 250, and 300 mg – Overall and By Subpopulation

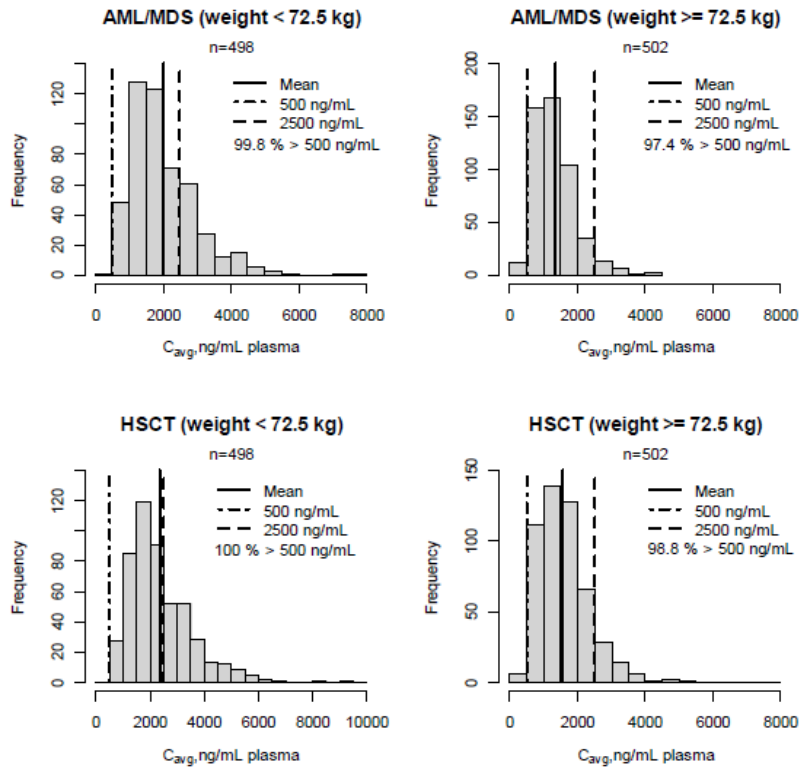
			Simulated dose level (mg) for the POS tablet		
Patient population	PK parameter		200	250	300
		range	% subject with POS exposure in range		
Overall	Cmin	<500 ng/mL	17.8	9.5	4.8
		>3750 ng/mL	0.75	2.2	3.2
	Cavg	<500 ng/mL	8	3.2	1
		≥500-<2500 ng/mL	86.3	84	80.1
		≥2500-<3750 ng/mL	4.5	9.6	14.3
		>3750 ng/mL	1.3	3.3	4.7
AML/MDS	Cmin	<500 ng/mL	21.4	11.9	6
		>3750 ng/mL	0.5	1.4	2.5
	Cavg	<500 ng/mL	10.4	4.1	1.4
		≥500-<2500 ng/mL	85.5	87.2	83.5
		≥2500-<3750 ng/mL	3.3	6	11.6
		>3750 ng/mL	0.8	2.7	3.5
HSCT	Cmin	<500 ng/mL	14.1	7	3.6
		>3750 ng/mL	1	3	3.9
	Cavg	<500 ng/mL	5.5	2.3	0.6
		≥500-<2500 ng/mL	87	80.7	76.6
		≥2500-<3750 ng/mL	5.7	13.1	17
		>3750 ng/mL	1.8	3.9	5.8

Boxplot comparing observed and simulated PK parameters in patients

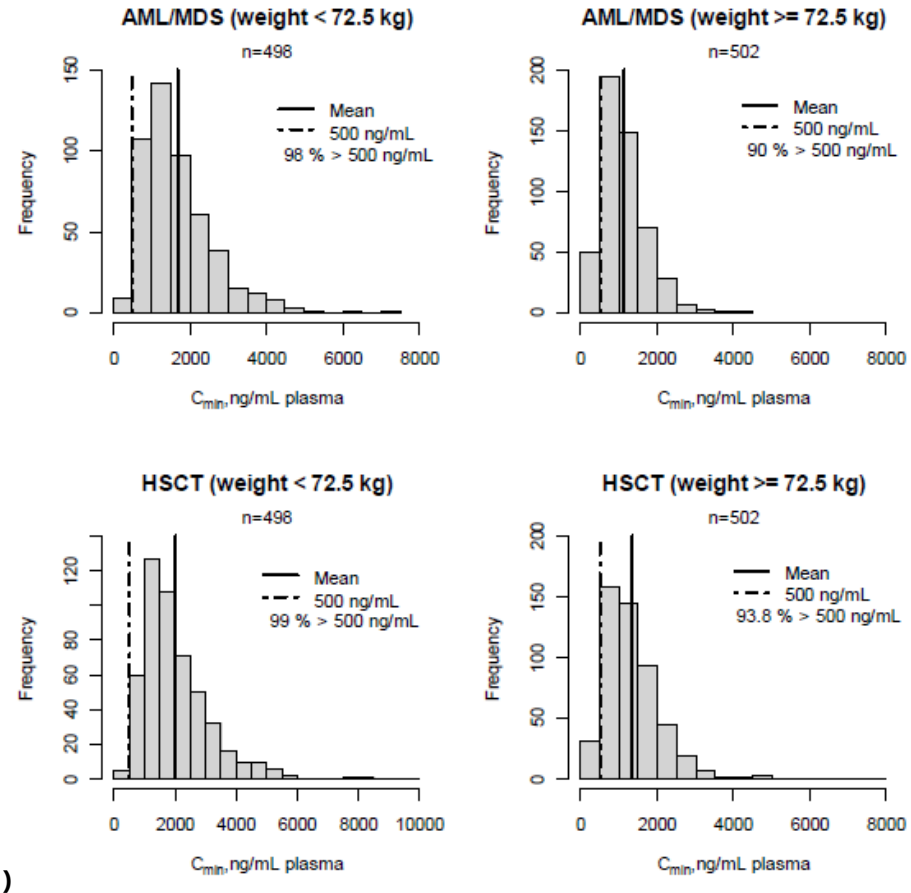


The population PK model developed for posaconazole tablet was used to simulate the pharmacokinetics of posaconazole in subjects at high risk for IFI and to assess the percentage of population with steady-state exposures above 500 ng/mL and 3750 ng/mL for 2 important parameters, Cavg and Cmin. In addition to 300 mg, alternate dose levels of 200 mg and 250 mg QD dosing (with BID dosing on Day 1) were simulated.

Distribution of simulated Cavg per subpopulation stratified by weight (300mg dose)



Distribution of simulated Cmin per subpopulation stratified by weight (300mg



)

The percentage of subjects with steady-state (Day 28) Cavg and Cmin below 500 ng/mL and above 3750 ng/mL, as simulated for the total and patient subpopulations, are depicted below (Table 7b.1 and Figure 7b.1).

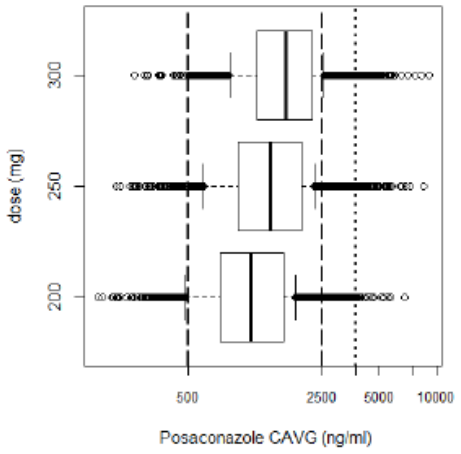
Table 7b.1 Simulated Percentage of Subjects with POS Exposures (Cmin and Cavg) below 500 ng/mL and above 3750 ng/mL for Doses of 200, 250 and 300 mg and per Subpopulation

			Simulated dose level (mg) for the POS tablet		
Patient population	PK parameter		200	250	300
		range	% subject with POS exposure in range		
Overall	Cmin	<500 ng/mL	17.8	9.5	4.8
		>3750 ng/mL	0.75	2.2	3.2
	Cavg	<500 ng/mL	8	3.2	1
		>3750 ng/mL	1.3	3.3	4.7
AML/MDS	Cmin	<500 ng/mL	21.4	11.9	6
		>3750 ng/mL	0.5	1.4	2.5
	Cavg	<500 ng/mL	10.4	4.1	1.4
		>3750 ng/mL	0.8	2.7	3.5
HSCT	Cmin	<500 ng/mL	14.1	7	3.6
		>3750 ng/mL	1	3	3.9
	Cavg	<500 ng/mL	5.5	2.3	0.6
		>3750 ng/mL	1.8	3.9	5.8

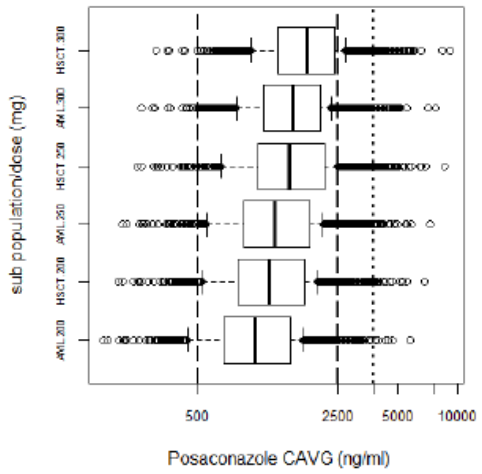
As there is no appreciable reduction in the proportion of subjects with very high exposures between the 250- and 300-mg dose and the known variability of posaconazole exposure would likely conceal any minor pharmacokinetic differences between these 2 doses, the MAH maintains that the 300-mg dose is the appropriate dose for consideration in both the prophylactic setting and as salvage therapy for refractory IFI.

Figure 7b1: Simulated Cavg after Multiple QD doses of 200, 250 or 300 mg (Following BID Dosing on Day1) Using the PopPK Model, when Given Without Regard to Food, in Total Population (7b.1a) and per Subpopulation (7b.1b).

7b.1a



7b.1b



Black line in box is median, box depicts the 25th and 75th quartiles, the whiskers depict the 0.3 x Inner quartile range (equivalent to 10th and 90th percentiles). Open dots represent individuals outside these 10 and 90th percentiles;

Comparisons of exposures after single doses of the oral suspension and the tablet formulation

In response to questions, the following comparisons were provided. For the single dose data, the observed concentration time profile for posaconazole tablet on Day 1, following 300 mg BID dose, is shown and compared with the observed concentration time profile for the posaconazole oral suspension on Day 3, following dosing as 200 mg QID (i.e., after 2 days of 200 mg QID dosing). This latter profile was selected because this is the best reflection of an early concentration-time profile with posaconazole oral suspension in patients at hand.

Figure 4.1 Mean (95% CI) observed posaconazole plasma concentration-time profiles following administration of 300 mg BID as POS tablet (Day 1) or 200 mg QID as POS oral suspension (Day 3, after 2 days of 200 mg QID dosing.

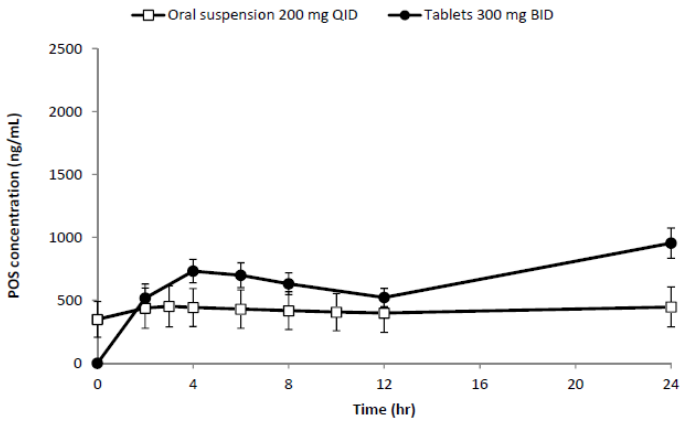
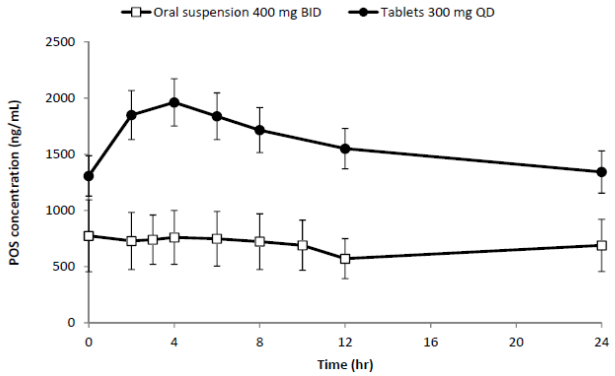


Figure 4.2 Mean (95% CI) observed posaconazole plasma concentration-time profiles following administration of 300 mg QD of POS tablet on Day 8 (after BID dosing on Day 1 only) or 400 mg BID of POS oral suspension on Day 10 (with 200 mg QID dosing for the first 3 days).



Additional Simulations to Evaluate Weight-based Dosing in Allogeneic HSCT Patients

Further simulations with the population PK model, developed for posaconazole tablet have been conducted in order to evaluate if a subgroup of patients may benefit from a lower dose (200 mg) of posaconazole tablet. As it was agreed that exposure differences between 250 and 300 mg were generally small, only the lower dose of 200 mg was further evaluated.

The simulation dataset included 1000 acute myelogenous leukemia/myelodysplastic syndrome (AML/MDS) subjects and 1000 HSCT subjects and the significant covariate (weight) identified during model development was included in the dataset. Three cut-off weights were chosen at the low end of the weight distribution, i.e. 50, 60 and 70 kg, representing approximately 5, 18 and 40% of the subjects included in the pivotal prophylaxis study of the posaconazole tablet (P05615). The simulations evaluated a 300 mg BID loading dose on Day 1 followed by 300 mg QD, and a 200 mg BID loading dose on Day 1 followed by 200 mg QD.

Table 1.1 Simulated Percentage of Subjects with POS Exposures (Cmin and Cavg) below 500 ng/mL and Cavg between 500 and 2500 ng/mL, 2500 and 3750 ng/mL and above 3750 ng/mL for the Daily Dose of 300 mg and when Weight Based Dosing is Applied for HSCT Patients at Different Weight Cutoffs

	% of patients with exposure				
Treatment[1]	Cmin < 500 ng/mL	Cavg < 500 ng/mL	Cavg between 500-2500 ng/mL	Cavg between 2500-3750 ng/mL	Cavg >3750 ng/mL
AML/MDS patients					
All on 300 mg	6.5	2.3	79.8	13.8	4.1
HSCT patients					
All on 300 mg	3.7	1.1	72.6	18.8	7.5
>50 kg on 300 mg ≤50 kg on 200 mg	4.1	1.1	74.3	18.0	6.6
>60 kg on 300 mg ≤60 kg on 200 mg	5.2	1.5	78.2	15.4	4.9
>70 kg on 300 mg ≤70 kg on 200 mg	6.6	1.7	83.7	11.4	3.2
All patients (AML/MDS patients + HSCT patients combined)					
All on 300 mg	5.1	1.7	76.2	16.3	5.8
AML on 300 mg HSCT >50 kg on 300 mg HSCT ≤50kg on 200 mg	5.3	1.7	77.1	15.9	5.4
AML on 300 mg HSCT >60 kg on 300 mg HSCT ≤60 kg on 200 mg	5.9	1.9	79.0	14.6	4.5
AML on 300 mg HSCT >70 kg on 300mg HSCT ≤70 kg on 200 mg	6.6	2.0	81.8	12.6	3.7

[1] The dose listed is BID on Day 1, following by QD for the next 27 days.
Cavg= AUC_{0-24}/24 at steady state

It is noted that the simulations are based on limited exposure data, in particular in the weight group ≤50 kg, and therefore the simulated exposures in this weight group are considered less reliable.

Further Simulations of the Effect of Food

Results of the food effect study with the final market image (FMI) of posaconazole tablet show that when a single dose of 300 mg of posaconazole tablet is administered with a high fat meal, posaconazole exposure (AUC(0-last)) increased 51%, as compared to the exposure of a single dose of 300 mg posaconazole tablet taken in a fasted state. When these data were included in the population PK model, the model describes a 56% increase in bioavailability when posaconazole tablets are taken

with a high fat meal, which is in concordance with the food effect that was observed in PN112. The estimated food effect is based on administration with a high fat meal which represents a worst case extreme of the potential food effect in patients receiving posaconazole as prophylaxis. It is likely that the food effect for lighter meals (i.e., lower fat) will be less than the ~50% effect observed. This effect is noteworthy because lighter meals are more typical for the patient population for whom this drug is indicated. By way of example, with posaconazole oral suspension (200 mg), AUC was increased by 2.6 to 3-fold with a low fat meal and 4-fold with a high fat meal.

It is not possible to simulate patient exposures with the population PK model under different food intake conditions, because the food status of patients included in P05615 is unknown. In fact the Applicant considers that it is likely that the range of exposures seen in P05615 actually captured the food effect in the target patient population, with exposures of AML/MDS patients and HSCT patients reflecting the lower and the higher end of the food effect, respectively. In study P05615, a ~30% higher plasma exposure of posaconazole was observed in HSCT patients as compared to neutropenic AML/MDS patients. Differences in plasma exposure between HSCT patients and the sicker, neutropenic AML/MDS patients may be related to their ability to take their dose with food (i.e., AML/MDS patients recently rendered neutropenic from cytotoxic chemotherapy also routinely suffer from severe nausea and anorexia, thereby limiting their food intake). Notably, the food effect largely falls within the moderate variability of posaconazole exposure in P05615 (CV% of approximately 40% in patients).

However, in order to address this question to some extent, significant assumptions with regard to food intake in the clinical trial P05615 were applied to population PK to facilitate further simulations. The population PK model was used to simulate the exposure (Cavg) of a typical HSCT patient weighing 50, 60, or 70 kg, receiving a 200 or 300 mg daily dose under different assumed food conditions. For the exposure estimation under different food scenarios, 2 significant assumptions were made. The first assumption was that during patient study P05615, each patient had taken posaconazole tablets with a high fat meal, and now for the simulation, the tablets are taken fasted (reducing the exposure with a factor representing a food effect of 1/1.56 (0.64) from the population PK model). The same was done for the exposure estimation for the second assumption of a fed condition, wherein it was assumed that each patient was dosed fasted during patient study P05615, and now for the simulation the tablets are taken with a high fat meal (increasing the exposure with a factor representing a food effect of 1.56 from the population PK model).

Table 1.4 Simulated exposures of a typical HSCT patient of different weights (50, 60 and 70 kg) and daily doses (200 mg and 300 mg) in different food intake conditions (assuming extreme food intake assumptions: the fasted state (factor 0.64), without regard to food intake (factor 1) and with a high fat meal (factor 1.56))

	Dose	Food	Cavg
50 kg			
HSCT	200 mg	0.64	1112
		1	1737
		1.56	2710
	300 mg	0.64	1670
		1	2605
		1.56	4064
60 kg			
HSCT	200 mg	0.64	921
		1	1440
		1.56	2246
	300 mg	0.64	1384
		1	2159
		1.56	3368
70 kg			
HSCT	200 mg	0.64	786
		1	1228
		1.56	1916
	300 mg	0.64	1181
		1	1842
		1.56	2874

Of note, in Table 1.4, the "1" value represents simulated exposures when posaconazole tablet was taken without regard to food (the actual food intake status in patient study P05615).

This table shows that, a HSCT patient weighing 50 kg, who now receives a dose of 200 or 300 mg with a high fat meal (assuming that he had fasted during study P05615), would obtain a Cavg of 2710 or 4064 ng/mL, respectively. As expected, for a patient weighing 60 or 70 kg, exposures with the same food intake condition/assumptions are lower. On the other hand, if a HSCT patient weighing 70 kg now receives a daily dose of 200 or 300 mg under fasting condition (assuming he had taken high fat meals during study P05615), the Cavg would be 786 or 1181 ng/mL, respectively. As expected, for a patient weighing 50 or 60 kg, exposures under the same food intake condition/assumptions are higher.

Applicability of data from the prophylaxis population to the treatment population

While a relatively lower dose of posaconazole oral suspension was used in the pivotal prophylaxis trials (600 mg/day) compared to the treatment dosing (800 mg/day), overlapping exposures have been seen in patients with these two treatment regimens.

Table 2-1 P05615 300 mg Dose Group, P01899, C/I98-316, and P00041 All Treated Subjects with PK Data Summary of Average Plasma Concentration

	P05615 300mg[a] n=186	P01899[b] n=194	C/I98316[b] n=252	P00041 n=232
Plasma Concentration				
n	186	194	252	232
Mean	1716.2	582.0	1103.2	839.8
Median	1530.0	485.7	914.8	679.0
STD	1090.6	375.1	743.7	699.0
Range	210.3 - 9135.0	92.1 - 1945.0	21.5 - 3650.0	5.8 - 3710.0
Cmin <=200	0	17 (9)	25 (10)	29 (13)
200 < Cmin< 500	10 (5)	85 (44)	30 (12)	58 (25)
500<=Cmin<=2,500	151 (81)	92 (47)	185 (73)	135 (58)
2,500<Cmin<=3,750	19 (10)	0	12 (5)	10 (4)
Cmin>3,750	6 (3)	0	0	0

a P05615 average plasma concentration is the Cmin

b P01899 and C/I98-316 average plasma concentration is the average of all samples collected in each study.

Source: P01899, C/I98-316, P05615, and P00041

The following table provides a dose-normalized comparison of the mean steady-state concentrations for the various doses of posaconazole oral suspension.

Table 2-2 POS Dose Normalized (to 1 mg Daily Dose) Mean Steady-State Concentrations from Patient Studies

Study	Dose of Oral Suspension, Dosing Frequency, Patient Population	POS Steady-State Concentration (ng/mL/Daily Dose)	
		Mean	%CV
P01899	600 mg/d (200 mg TID), Prophylaxis in neutropenic oncology patients	0.972	65
P01893[a]	800 mg/d (400 mg BID), rIFI/febrile neutropenia	0.904	86
P00041[a]	800 mg/d (200 mg QID, followed by 400 mg BID), Treatment of rIFI	1.05	83
C/I98-316	600 mg/d (200 mg TID), Prophylaxis in HSCT patients with GvHD	1.87	67

a: Steady-state Cavg value, patient study listed for PK comparison.

Abbreviations: BID=twice daily, Cavg=average plasma concentration, CV=coefficient of variation, GvHD=graft-versus-host disease, HSCT=hematopoietic stem cell transplant, mg/d=milligrams per day, ng/mL=nanogram per milliliter, POS=posaconazole, QID=four times daily, rIFI=refractory invasive fungal infection, TID=three times daily.

Source: P01899, P01893, P00041, and C/I98-316

The demographic characteristics were also similar among the three pivotal trials of posaconazole oral suspension (including the 2 trials in prophylaxis [P01899, C/I98-316] and 1 trial in treatment of IFI [P00041]) and the more recent posaconazole tablet study in prophylaxis (P05615).

2.5.2. Main study (P05615)

Pharmacokinetics and safety of solid oral posaconazole (SCH 56592) in subjects at high risk for invasive fungal infections.

Methods

This was a two-part, sequential, single-arm, open-label, multicenter, global study of the pharmacokinetics and safety of posaconazole tablet when used as prophylaxis in adult subjects at high risk for invasive fungal infections (IFIs). The study was conducted between 2009 and 2012. Patients were enrolled in 42 study centres in 15 countries:

The primary objective of this study was to characterize the pharmacokinetic (PK) profile of posaconazole tablet in a representative subject population. The secondary objectives of this study were (1) to evaluate the safety and gastrointestinal tolerability of posaconazole tablet in a representative subject population, and (2) to evaluate the steady-state posaconazole exposure in a representative population given posaconazole tablet.

The study consisted of sequential parts 1A, 1B and 2.

Part 1 enrolled neutropenic subjects undergoing chemotherapy for acute myelogenous leukemia (AML) or myelodysplasia (MDS). The treatment duration was to be up to 28 days, with a minimum duration of therapy of 8 days and a maximum duration of 28 days. Two different dosing groups were evaluated in Part 1.

Part 1A: 200 mg BID on Day 1, followed by 200 mg QD thereafter

Part 1B: 300 mg BID on Day 1, followed by 300 mg QD thereafter

The dose selection and decision to proceed to Part 2 were based on the posaconazole tablet exposure levels achieved and the safety observed among the Part 1 subjects.

Part 2 enrolled two patient populations. Neutropenic subjects undergoing chemotherapy for AML or MDS and subjects who were recipients of allogeneic hematopoietic stem cell transplant (HSCT).

Study Participants

Eligible children were to be aged ≥ 18 years weighing more than 34kg with Anticipated (likely to develop within 3 days to 5 days) or documented prolonged neutropenia (absolute neutrophil count [ANC] <500/mm3 [0.5 x 10^9/L]) at baseline and likely to last for at least 7 days due to standard intensive induction chemotherapy.

The targeted sample size was 210 subjects. The determination of sample size was based upon the targeted number of subjects for evaluation of PK and safety as well as the anticipated discontinuation rate.

The posaconazole plasma concentration-time data was determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method

In the study, there were a total of 230 treated subjects, 20 subjects were treated with posaconazole tablet 200 mg (Part 1A), and 210 subjects were treated with posaconazole tablet 300 mg (Part 1B, n=34; Part 2, n=176).

A total of 237 subjects were screened for eligibility. 27 subjects who were screened but not enrolled (22 subjects) (i.e., screen failures) or enrolled but not treated (5 subjects). Failure to meet protocol eligibility criteria was the primary reason for which subjects were not enrolled

Outcomes

Clinical failure during the exposure was the secondary efficacy endpoint collected. There was no adjudication or review of IFI diagnosis. The reported IFI diagnosis was based upon investigator judgment.

In the 200 mg Cohort, IFIs (proven or probable as determined by the investigator) were reported for 2 subjects (10%) treated with posaconazole. Both subjects with an IFI in the 200-mg dosing cohort (Part 1A) died as a result of the infection within the protocol-defined follow up period of 65 days. The Cmin values for these patients were reportedly 261ng/ml and 162ng/ml Cavg was not reported. There were no further deaths in the 200 mg Cohort.

In the 300 mg Cohort, there was 1 subject (<1%) treated with posaconazole with a reported IFI (proven or probable as determined by the investigator). This subject was diagnosed with a fungal infection of the pleura (with abnormal radiograph on Day 8). Culture results reported the isolation of *Candida glabrata*. The subject's posaconazole concentration at the time of diagnosis of the infection was 2530 ng/mL.

There were 9 additional subjects in the 300 mg Cohort identified by the investigator with a "possible" IFI. Abnormal radiographic findings were reported for all subjects with a diagnosis of a “possible” IFI; no mycological evidence of infection was identified in these subjects. In all cases, the investigator reported the presence of possible IFI for the analysis of clinical failure.

The incidence of AEs associated with discontinuation of study drug was 18% for subjects in the 300-mg dosing cohort. Early treatment discontinuation due to a possible IFI occurred with six (3%) out of the 18 subjects. Eighteen (9%) of the treated subjects were not alive at Day 65, the majority of which occurred in Part 2 of the study. Note there were two additional 300 mg subjects that had reported deaths after the Day 65 window (>70 days).

2.5.3. Discussion on bridging strategy, pharmacokinetics and exposure in patients and clinical efficacy

Bridging strategy

The PK/PD relationship for azoles in general and for posaconazole in particular has been studied in a murine model for candidiasis and a rabbit model of invasive pulmonary aspergillosis. For *Candida*, the PK/PD parameter most closely related with outcome in a murine model was shown to be AUC24/MIC. The Cmax/MIC ratio was also shown to be relevant. In clinical studies plasma concentration rather than AUC/MIC ratios have been used in an attempt to correlate exposure and response and Cavg is used as the bridging parameter. The plasma concentration curve for posaconazole at steady state is relatively flat due to the long half- life, and Cavg and AUC can be used interchangeably. Cavg is

derived by dividing AUCtau/tau.

Scientific advice had been obtained from CHMP for the development of an intravenous solution of posaconazole. A development programme focusing on PK and exposure similarity between the approved formulation of posaconazole (oral suspension) and the proposed new formulation was agreed in principle.

Exposure- response analysis from the pivotal trials for the oral suspension had indicated an association between lower plasma concentrations and clinical failure. The lower boundary (Cavg > 500 ng/mL) for the pivotal tablet study (P05615) was selected based on the results of the exposure/ response analyses from studies with the oral suspension. While a exposure- response relationship seems plausible, and is supported by some in vitro data, clinical data are sparse. A clear target is difficult to establish. There is no identified exposure level separating clinical response from failure. In the pivotal prophylaxis trials mean Cavg were 583 ng/mL with 90% of patients attaining posaconazole average plasma levels (Cavg) ≥228 ng/mL (study P01899) and 1130 ng/mL with 90% attaining posaconazole plasma Cavg greater than or equal to 322 ng/mL (study C/I98-316). In the treatment trial, clinical results were best for patients in the 4th quartile, which had a steady-state Cavg mean of 1250 ng/mL.

It is agreed that the outcome in the upper exposure quartiles is better than in the lowers quartiles in the treatment study P00041. Due to the low number of events in the prophylaxis trials, such a trend is more difficult to detect. For this reason data were reviewed by using a composite endpoint as proposed by the FDA, which provided support for the 500ng/ml lower boundary. This method certainly increases the event rate, however by including mortality it does at the same time introduce further uncertainty in the evaluation, as this population has a relatively high mortality unrelated to fungal infections and their treatment.

For the pivotal study with the tablet formulation, a target range of Cavg between 500- 2500 ng/ml was aimed for in 90% of subjects, as discussed in the CHMP scientific advice. Considering all the data presented, and acknowledging the inherent difficulties, it seems reasonable to accept the proposed 500ng/ml threshold as the lower boundary for both treatment and prophylaxis indication.

The rationale for the upper boundary of the 500- 2500ng/ml target range targeted for 90% of the population was not well explained. While around half of the healthy volunteers had exposures around 2500 ng/ml or greater, less than 5 % of patients had such exposures. The absolute upper boundary (Cavg < 3,750 ng/mL) was selected based on preclinical toxicology findings, specifically considering a possible effect of posaconazole on steroidogenesis, although the NOEL (Cavg 975ng/ml) for such an effect in monkeys is seen within the therapeutic range in humans and seems hence difficult to justify. Less than 7.5% of the healthy volunteers had exposures around 3750 ng/ml or greater, and such exposures had not been observed in any patient trials with the oral suspension.

PK and exposure – study P05615

This single arm Phase 1/III study aimed to establish the PK profile of the posaconazole tablet formulation and to provide bridging data to the oral suspension. Posaconazole tablets were given without regard to food in this study and food intake was not recorded. Two dose levels, 200mg and 300mg, were investigated using two different tablet formulations (C and D).

Dense sampling was performed in all patients in part 1 and a subset of part 2 patients. Sparse sampling (Cmin) was performed in the remaining subjects in Part 2.

Data from dense (serial) sampling are available from 68 patients, of which n=17 were HSCT patients receiving a dose of 300mg and 51 patients with AML or MDS who received doses of 200mg (n=18) or 300mg (n= 33). The 2 groups were analysed separately as in studies with posaconazole oral suspension, exposure was shown to be higher in patients with HSCT.

At the 200mg dose level, investigated only for the group with the expected lower exposure (AML/MDS), PK target criteria were not met. At a dose of 300mg, 90% of AML/ MDS patients were within the target range of 500- 2500nm/ml, the remaining 10% had exposures > 2500 but < 3750ng/ml, meeting the predefined criteria.

There was a strong correlation between Cmin and Cavg in part 1 of the study. In part 2, sparse sampling (Cmin) only was performed, and Cavg was predicted based on this correlation (pCavg). The Cmin evaluable cohort included 205 patients. Here, predicted mean Cavg levels for 200 mg and 300 mg (1010 ng/mL and 1970 ng/mL) were higher than in the group of serial PK-evaluable subjects (1970 ng/mL vs. 1580 ng/mL in the). This may in part be due to an overestimation of Cavg in the upper exposure range and in part reflect a real difference between the populations as the underlying conditions differ.

The lower limit exposure criteria were met; however the upper bound was exceeded. At a dose level of 300mg, > 99% of had plasma concentrations of Cavg > 500ng/ml. However, 15% of patients had exposures > 2500 ng/ml, and 4% exceeded the upper threshold of 3750ng/ml. As expected from data with the oral suspension, HSCT patients had higher exposures on average an exceeded the target range more frequently.

The MAH developed a population PK model, which was used to simulate 1000 HSCT and AML patients each, taking the identified relevant covariate of weight into account. The modelled data are in line with the study results. The upper end of the targeted range is exceeded in a relevant proportion of subjects. Patients after HSCT patients and or those weighing <72.5 kg are more likely to exceed the target exposure range.

As the upper exposure target was exceeded with the 300mg dose, additional modelling was requested to evaluate doses < 300mg. These simulations indicate that the 200mg dose would indeed be expected to result in lower than targeted exposures in 8% of patients overall, while this number is reduced to 3.3% with 250mg and to 1% with the 300mg dose. The aim of the development program was the increase exposure and efficacy, which is justified by the high morbidity and mortality of IFI when they occur. The figures indicate that from an efficacy perspective, a dose of 300mg may be preferable, as may be expected. It should however be remembered that the target exposure is derived from a limited dataset and the chosen cut-off of 500ng/ml is not a clear margin separating success from failure.

Simulation results presented with the responses show that there is indeed a relatively small difference between patients achieving exposures > 3750 ng/ml between the 250mg and 300mg dose overall. The dose of 300mg may be the most appropriate dose at least for a proportion of patients. Apart from the underlying disease, weight has also been identified as a relevant covariate and a weight cut-off for a lower dose may decrease the number of patients with high exposures with relevantly affecting the lower margin. Further simulations requested explored if this dose should be applicable to the whole target population. Those simulations suggested that a lower dose of 200mg in HSCT patients < 60 or

70kg would lead to a lower proportion of patients exceeding the upper target range, although the difference is comparatively small. Separating the posology by weight alone would have been practicable; however, separating the dose in addition by weight seems less appropriate, in particular as it is not clear how other immunosuppressed patients not falling in either category should be treated (where posaconazole is used as a treatment, the target population includes all patients with an IFI).

An added complicating factor is the observed food effect for the tablet formulation. In the pivotal study posaconazole tablets were given without regard food, yet the food effect study submitted with the responses indicates a 50% increase in AUC with a high fat meal. The effect may be less in clinical practice, where the majority of the target population may not take high fat meals, but it is not known how lighter meals may have affected exposure. The applicant's position was that the effect of food is largely captured in the range of exposures seen due to the differences in food intake between the populations, which is likely correct to some extent. Additional simulations, covering the more extreme ends of the food related exposure spectrum were provided, showing that the risk of underexposure is below that seen with the presently approved formulation. A wording pointing out that exposure is increased by food intake is added to the SmPC.

Applicability of data from the prophylaxis population to the treatment population

While there are some uncertainties about the exposure targets in general, it is accepted in principle that the exposure targets set for the prophylaxis indication may be applied to the treatment indication based on the available data. However, several factors may lead to differences in exposure between prophylaxis and treatment populations: e.g. patients with rIFI may require different doses to achieve similar exposures due to reduced absorption due to the acute infection or PK parameters affecting exposure (such as Vd, CL) may be altered in acute infection. There may also be differences in concomitant medication. The currently approved dose for the oral suspension for the treatment rIFI is 800mg/ day, while the approved dose for prophylaxis is 600mg/day. Despite the different doses, there is overlap in the resulting exposure between study 041 (treatment of IFI) when compared to 316 (prophylaxis of IFI), which might suggest higher doses may be needed in the treatment population than in the prophylaxis indication to achieve similar exposures. When dose normalised exposures are compared, it appears that there is little difference between mean exposure in the treatment study, which included patients with AML/MDS and HSCT (and others), and study P01899 (AML/MDS only), while mean exposure is lower than in trial 316 (HSCT only). The relative proportion of patients with HSCT or AML/MDS in study P00041 will have affected the overall result, and separate evaluation of these subgroups would contribute to the understanding of the comparative exposure.

The main difference between the exposure not only in these subpopulations, but also between the treatment and the prophylaxis population, is considered to lie in the different ability to comply with dietary requirement, which is plausible. It is agreed that the reduced food effect seen with the tablet formulation can be expected to reduce the differences between the groups and provides support for the view that the same dose may be appropriate for both. The applicant provided data to suggest that the pathophysiological changes during infection are not likely to lead to relevant difference in exposure in the treatment population.

Clinical efficacy

This open, non-comparative study was not designed as a clinical efficacy study, but aimed to investigate the PK of the proposed tablet formulation of posaconazole in the target population for the prophylaxis indication and to provide additional safety data. The study population included patients

with AML/MDS and HSCT with the aim to enrol patients representative of the target population for antifungal prophylaxis with posaconazole. A tabulated comparison of the baseline demographics between P05615 and the trials with the oral suspension indicated that the populations appear similar, and while some of the baseline covariates of possible relevance to exposure data were not evenly distributed between the studies (gender, race) as may be expected, these factors were not consistently shown to be relevant in the composite PK analysis.

A PK target range of Cavg was set for study part 1, based on the results from previous trials with the oral suspension as a surrogate for the clinical outcome and PK results have been discussed earlier. The study design including lack of a control group and short study duration may be acceptable with regards to the primary endpoint, but limits safety data evaluation. The criteria for diagnosis of an IFI were not clearly presented and not adjudicated.

The reported rate of breakthrough fungal infections was low. In the 200mg dose group, 2 of 20 patients were clinical failures, and 1 failure occurred in the 300 mg dose group. Nine patients were identified to have possible infections; in 6 of these cases posaconazole was discontinued. Of the 8 cases which suspected or proven IFI for which plasma concentration values were available, 4 were below the exposure target of 500ng/ml, and 4 above. Available data are too limited to draw conclusions.

In the pivotal prophylaxis trials in HSCT patients (C/I98-316), the reported IFI rate at 16 weeks was 5% (16/301 subjects) with an average duration study drug of 84 days. The incidence of IFI in the pivotal trial in AML/MDS with posaconazole oral suspension (P01899) was 7/304 (2%); the average duration of treatment for subjects in this study was 22 days, but follow up was longer than in P05615.

In summary, the reported incidence of IFI in this trial was low and appeared in line with earlier prophylaxis trials with the oral suspension, however treatment duration and follow up was shorter than in previous trials. As expected, no firm conclusions can be drawn from these results.

2.5.4. Conclusions on bridging strategy, pharmacokinetics and exposure in patients and the clinical efficacy

The generated data suggest an exposure/response relationship, and such a relationship is biologically plausible. The lower boundary of 500ng/ml is an acceptable lower exposure target based on the limited data available. It does however not represent a cut-off clearly separating success from failure. The acceptability of the upper exposure target depends on the observed safety.

Simulation results suggest that a dose of 300mg may be the most appropriate dose for the majority of patients. A lower dose of 200mg could reduce the proportion of HSCT patients <60kg exceeding the target range of Cavg. In view of the relatively small difference, the lack of confirmed safety problems from the available database so far, and the practical difficulties separating subpopulations explained earlier it seems preferable to apply the 300mg dose to the whole target population.

The omission of recording the food effect in the pivotal study remains a flaw in the development programme of the tablet formulation, and the CHMP recommends that further information should be obtained in the on-going trial.

2.6. Clinical safety

A total of 334 subjects treated with posaconazole tablet were enrolled in clinical studies to support the registration of posaconazole tablet. This included 104 healthy volunteer subjects, who were enrolled in five Phase 1, single and multiple dose studies and 230 patients, who received a daily dose of either 200mg or 300mg. Safety data were collected for all randomized subjects who took at least one dose of posaconazole or placebo to posaconazole.

Safety data in healthy volunteers as summarised by the MAH are presented below:

Of the 31 healthy volunteers who received multiple daily doses of posaconazole tablets of 200 mg, 300 mg, or 400 mg following a BID loading dose on Day 1, 4 subjects (13%) discontinued treatment due to an AE that was considered possibly or probably related to study drug. The most common reported TEAEs after multiple dosing were hepatic enzyme increased (23%, all considered mild or moderate), diarrhoea (19%), and nausea (13%) which were all considered treatment related. There were no deaths or SAEs in any of the studies of healthy. The safety profile of posaconazole tablets in healthy volunteers was similar to the safety profile of posaconazole oral suspension in healthy volunteers.

The overview focuses on the data from the 210 patients who received the proposed dose of 300mg/ day, for further data on the 200mg dose group (n=20) please see the Clinical assessment report.

Patient exposure

In the 300 mg cohort (n= 210), the mean and median duration of therapy was 23 and 28 days.

Treatment Duration, days[a]	Number of Subjects (n,%) All Treated Subjects 300 mg Cohort n=210
Received Any Treatment	210 (100)
≥1 Day	210 (100)
≥2 Days	207 (99)
≥3 Days	205 (98)
≥8 Days	193 (92)
≥14 Days	178 (85)
≥21 Days	151 (72)
>28 Days	21 (10)

Treatment Duration, days[a]	Number of Subjects (n,%) All Treated Subjects 300 mg Cohort n=210
Statistics (day)[b]	
Number of Subjects	210
Mean (SD)	22.7 (8.1)
Median	28
Minimum, Maximum	1, 30

[a] n=number of subjects; POS=posaconazole; SD=standard deviation.

[b] Duration is based on treatment begin date and treatment end date and does not take into account possible dosing interruptions and subject noncompliance.

[c] Statistics are exclusive of subjects not treated and subjects with an unknown duration.

Adverse events

In the 300mg cohort, nearly all subjects (99%) experienced at least one TEAE, the most common TEAEs (≥ 20% of subjects) included diarrhoea (29%), pyrexia (28%), nausea (27%), hypokalaemia (22%), and febrile neutropenia (20%). 40% experienced a treatment-related TEAE, the most common (>5% incidence) were nausea (11%) and diarrhoea (8%).

	Number of Subjects (n,%) All Treated Subjects POS Tablet 300 mg Cohort n=210
Treatment-Emergent Adverse Events	207 (99)
Treatment-Related Treatment-Emergent Adverse Events	84 (40)
Serious Adverse Events	69 (33)
Deaths	20 (10)
Severe/Life-Threatening Treatment Emergent Adverse Events	111 (53)
Study Drug Discontinuation Due to an Adverse Event	38 (18)

In comparison, in the two randomized, comparative prophylaxis studies (P01899 and C/I98-316) of posaconazole oral suspension that enrolled a similar population to that enrolled in P05615, the most frequently reported TEAEs were fever (posaconazole: 45%, FLU: 47%), diarrhoea (posaconazole: 42%, FLU: 39%), and nausea (posaconazole: 38%, FLU: 37%). The most common treatment-related TEAEs were nausea (posaconazole: 7%, FLU: 8%), diarrhoea (posaconazole: 5%, FLU: 4%), and vomiting (posaconazole: 4%, FLU: 5%).

Serious adverse event / deaths / other significant events

The most common AEs leading to death were from "infections and infestations", reported in 8 subjects (including sepsis and septic shock), and there were 2 subjects with reported renal failure as an AE leading to death. All of the AEs leading to death in the 20 subjects were reported as unlikely related to study drug.

SAEs were reported for 69 (33%) of the 300 mg cohort. The most common SAE terms reported (≥4 subjects) were 11 subjects with febrile neutropenia (5%), 5 subjects with sepsis (2%), and 4 subjects with diarrhoea (2%). SAEs considered related to posaconazole were reported for 6 (3%) patients. There were 2 (1%) subjects with treatment related SAEs of increased blood creatinine and drug reaction (suspected DDI with cyclosporine), 2 (1%) SAEs of abnormal liver function tests, 1 (<1%) subject with hepatotoxicity, and 1 (<1%) subject with renal failure.

Discontinuation due to adverse events

The incidence of AEs associated with discontinuation of study drug was 18% for subjects in the 300 mg Cohort. There were 6 (3%) subjects with treatment failure that resulted in early treatment discontinuation. AEs considered related to posaconazole were reported in 11 (5%). The most common AEs (≥3 subjects) that led to discontinuation of study drug were nausea (2%), fungal infection (1%), and liver function test abnormal (1%).

Table Summary of Adverse Events Considered Related to Posaconazole Tablet and Leading to Study Drug Discontinuation, All Treated Subjects, Posaconazole Tablet - 300 mg Cohort

System Organ Class Preferred Term	Number of Subjects (n,%) All Treated Subjects 300 mg Cohort n=210
Cardiac Disorders	1 (<1)
Sinus Bradycardia	1 (<1)
Gastrointestinal Disorders	2 (1)
Nausea	2 (1)
Hepatobiliary Disorders	2 (1)
Hepatic Function Abnormal	1 (<1)
Hepatotoxicity	1 (<1)
Immune System Disorders	1 (<1)
Graft Versus Host Disease	1 (<1)
Investigations	4 (2)
Electrocardiogram QT Prolonged	1 (<1)
Liver Function Test Abnormal	3 (1)
Skin And Subcutaneous Tissue Disorders	1 (<1)
Rash Pruritic	1 (<1)
Vascular Disorders	1 (<1)
Hypertension	1 (<1)
BID=twice daily; Q12hr= every 12 hours, QD=once daily; n=number of subjects; POS=posaconazole.	

Adverse events of special interest

Hepatic Adverse Events

Liver function test abnormality or hepatic enzyme increase were reported for 9 (4%) subjects treated as a part of the 300 mg Cohort. Seven (3%) of the subjects with liver function test abnormality or hepatic enzyme increase were classified by the investigator as having a related TEAE. Three of these 7 (1%) subjects with a related TEAE of liver function test abnormality were discontinued from study.

In addition to the 9 subjects with abnormal liver function tests or enzymes, hepatic TEAEs were reported by 10 (5%) subjects. This included 1 subject with hepatotoxicity TEAEs reported in both SOC categories. Four (4) (2%) subjects experienced severe or life-threatening hepatic TEAEs. Two met study criteria for Hy's Law. Three of the subjects described above were considered to have hepatic TEAEs possibly related to study drug, this included I case meeting Hy's law criteria, one case of abnormal liver function test, and one case of "cytolytic" hepatitis, classed as severe.

Cardiovascular events including ECG abnormalities

In the 300 mg Cohort of P05615, cardiovascular TEAEs were reported by 11 (5%) subjects. Three subjects had a cardiovascular TEAE that were judged to be related to study therapy. This included 2 subjects with QTc prolongation >500, which was though the be study drug related, was associated with bradycardia and led to discontinuation in one case. Posaconazole trough concentration peaked at 811 ng/mL on Day 3.Two cardiovascular events were reported as SAEs and led to drug discontinuation and death, but both of these were considered unlikely related to study drug.

Table Summary and Listing of Abnormal QTc Values and/or Changes from Baseline, All Treated Subjects, Posaconazole Tablet - 300 mg Cohort

	Count/Number of Subjects/ Number of Subjects Evaluable (n/N,%) All Treated Subjects 300 mg Cohort n=210		
	Any QTc	Bazett QTc	Fridericia QTc
Change from Baseline >60 msec[a]	14/208 (7)	9/208 (4)	11/208 (5)
Treatment Phase Value >500 msec[b]	3/208 (1)	3/208 (1)	1/208
Males – Treatment Phase Value ≥450 msec[b]	41/130 (32)	41/130 (32)	24/130 (18)
Males – Change from Baseline ≥60 msec to ≥450 msec[a]	7/130 (5)	5/130 (4)	5/130 (4)
Females – Treatment Phase Value ≥470 msec[b]	11/78 (14)	11/78 (14)	6/78 (8)
Females – Change from Baseline ≥60 msec to ≥470 msec[a]	3/78 (4)	1/78 (1)	3/78 (4)

[a] n=number of subjects; POS=posaconazole.

[b] Denominator based on subjects with a Baseline value and at least one Treatment Phase value.

[c] Denominator based on subjects with at least one Treatment Phase value.

Gastrointestinal events

In the 300 mg Cohort of P05615, the most commonly reported gastrointestinal AEs included diarrhoea (29%), nausea (27%), vomiting (13%), abdominal pain (11%), and constipation (10%). A total of 54 (26%) subjects experienced gastrointestinal AEs considered related to study drug. Of these, the most commonly reported events were nausea (11%) and diarrhoea (8%). Ten (10) (5%) subjects reported gastrointestinal AEs that led to study drug discontinuation. The most commonly reported gastrointestinal AEs that led to study drug discontinuation were nausea (2%) and diarrhoea (1%). There was one gastrointestinal AE (neutropenic colitis) that led to death. This event was not considered by the investigator to be related to study drug.

Laboratory findings

For ALK-P, ALT, AST, and total bilirubin, the majority of subjects' baseline values were Grade 0. For ALK-P and total bilirubin, the majority of subjects' values remained at Grade 0 throughout the study of the 300 mg Cohort. The largest shifts were three grade shifts, from Grade 0 to Grade 3 in 1 subject for ALK-P and 4 (2%) subjects for total bilirubin. For ALT, the majority of subjects' values either remained at Grade 0 (84 [40%] subjects) or had a minor shift of 1 grade (59 [28%] subjects from Grade 0 to Grade 1). For AST, the majority of subjects' values either remained at Grade 0 (110 [52%] subjects) or had a minor shift of 1 grade (61 [29%] subjects from Grade 0 to Grade 1). The largest shifts that occurred for ALT and AST were four grade shifts, from Grade 0 to Grade 4 in 1 subject for ALT or AST.

There were 2 subjects, Subject No. 2/000179 and 50/000072, in the 300 mg Cohort of P05615 that met the protocol pre-specified criteria for significant hepatic effect consistent with Hy's law (ALT and/or AST ≥ 3X ULN with ALK-P ≤ 2X ULN and total bilirubin ≥ 2X ULN without evidence of bilirubin obstruction. In the subject with possibly posaconazole related LFT derangedment meeting Hy's law

criteria, posaconazole trough concentration peaked at 1020ng/ml, in the second subject (Probable relationship) posaconazole Ctrough peaked at 783 ng/ml.

Table Changes from Baseline (Grades 0, 1, or 2) to Worst (Grades 3 or 4) By CTC Grade During Treatment, Liver Function Tests, All Treated Subjects, Posaconazole Tablet - 300 mg Cohort

Laboratory Group	Laboratory Parameter	Number of Subjects /Number of Subjects Evaluable (n/N,%) All Treated Subjects 300 mg n=210
Chemistry	ALK-P (U/L)	1/209 (<1)
	ALT (U/L)	11/208 (5)
	AST (U/L)	4/208 (2)
	Total Bilirubin (µmol/L)	5/208 (2)
ALK-P=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; n=number of subjects, N=number of subjects with a baseline value and at least one other value obtained during the treatment phase for each laboratory parameter.		

For selected electrolytes, the largest shifts that occurred for hyperkalaemia, hypernatraemia, and hyponatraemia varied from one to four grade shifts. The largest shifts that occurred for hypokalaemia were three grade shifts, Grade 0 to Grade 3 in 18 (9%) subjects.

Table Changes from Baseline (Grades 0, 1, or 2) to Worst (Grades 3 or 4) By CTC Grade During Treatment, Selected Electrolytes All Treated Subjects, posaconazole **aconazole Tablet - 300 mg Cohort**

Laboratory Group	Laboratory Parameter	Number of Subjects/ Number of Subjects Evaluable (n/N,%) All Treated Subjects 300 mg n=210
Chemistry	Hyperkalaemia (mmol/L)	6/209 (3)
	Hypokalaemia (mmol/L)	26/209 (12)
	Hypernatraemia (mmol/L)	0/209
	Hyponatraemia (mmol/L)	6/209 (3)
CTC=Common Toxicity Criteria; n=number of subjects, N=number of subjects with a baseline value and at least one other value obtained during the treatment phase for each laboratory parameter.		

For creatinine, the majority of subjects' baseline values were Grade 0, and the majority of subjects' values remained at Grade 0 throughout the study. The largest shift that occurred was a three grade shift, Grade 0 to Grade 3, for 1 subject.

Safety related to drug-drug interactions and other interactions

The posaconazole interactions seen with posaconazole oral suspension are also expected to occur with the posaconazole tablet. As has been shown with other azole antifungals, posaconazole is an inhibitor of the cytochrome P450 enzyme CYP3A4 at clinically relevant concentrations and, thus, possesses the potential for drug interactions with concomitantly administered drugs metabolized by CYP3A4. In vivo, posaconazole does not significantly inhibit other human CYP450 enzymes including CYP1A2, CYP2E1, CYP2C8/9 and CYP2D6. posaconazole does not have any major circulating metabolites and its

concentrations are unlikely to be altered by inhibitors and/or inducers of CYP450 enzymes. posaconazole is metabolized via UDP-glucuronosyltransferase (Phase 2 enzymes); therefore, inhibitors or inducers of this clearance system may affect posaconazole's plasma concentrations. Posaconazole is a substrate and inhibitor of the transporter P glycoprotein (PgP), so inhibitors or inducers of the PgP system may affect posaconazole 's.

Exposure based analysis of safety data

Table 14-1 Summary of Treatment-Related Treatment-Emergent Adverse Events by Quartile of pCavg Values, All Cmin PK-Evaluable Subjects, POS Tablet - 200 mg and 300 mg Cohorts Combined (Protocol No. P05615)

	pCavg Mean (ng/mL)	pCavg Range	No. of Subjects	No. of Subjects Reporting Any Adverse Event
Quartile 1	860 ng/mL	442 ng/mL to 1223 ng/mL	51	29 (57)
Quartile 2	1481 ng/mL	1240 ng/mL to 1710 ng/mL	51	19 (37)
Quartile 3	1979 ng/mL	1719 ng/mL to 2291 ng/mL	51	16 (31)
Quartile 4	3194 ng/mL	2304 ng/mL to 9523 ng/mL	52	20 (38)

n=number of subjects; pCavg= predicted average concentration from Cmin; POS=posaconazole.
Source Data: P05615

Table 14-2 Summary of Treatment-Related Treatment-Emergent Adverse Events by Quartile of pCavg Values, Incidence ≥ 2% Among All Cmin PK-Evaluable Subjects, POS Tablet - 200 mg and 300 mg Cohorts Combined (Protocol No. P05615)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Total
pCavg Mean	860 ng/mL	1481 ng/mL	1979 ng/mL	3194 ng/mL	1885 ng/mL
pCavg Range	442 ng/mL to 1223 ng/mL	1240 ng/mL to 1710 ng/mL	1719 ng/mL to 2291 ng/mL	2304 ng/mL to 9523 ng/mL	442 ng/mL to 9523 ng/mL
Number of Subjects	n=51	n=51	n=51	n=52	n=205
Adverse Event					
Nausea	5 (10)	5 (10)	3 (6)	7 (13)	20 (10)
Diarrhoea	6 (12)	3 (6)	6 (12)	2 (4)	17 (8)
Abdominal Pain	4 (8)	3 (6)	2 (4)	1 (2)	10 (5)
Vomiting	3 (6)	3 (6)	0	4 (8)	10 (5)
Alanine Aminotransferase Increased	2 (4)	2 (4)	4 (8)	1 (2)	9 (4)
Hypokalaemia	3 (6)	0	3 (6)	2 (4)	8 (4)
Rash	5 (10)	1 (2)	1 (2)	1 (2)	8 (4)
Aspartate Aminotransferase Increased	0	2 (4)	3 (6)	2 (4)	7 (3)
Abdominal Pain Upper	2 (4)	1 (2)	1 (2)	2 (4)	6 (3)
Dyspepsia	1 (2)	2 (4)	3 (6)	0	6 (3)
Hypophosphataemia	3 (6)	1 (2)	1 (2)	1 (2)	6 (3)
Liver Function Test Abnormal	2 (4)	2 (4)	0	1 (2)	5 (2)
Decreased Appetite	1 (2)	2 (4)	0	1 (2)	4 (2)
Flatulence	1 (2)	1 (2)	2 (4)	0	4 (2)
Hypomagnesaemia	2 (4)	1 (2)	0	1 (2)	4 (2)

n=number of subjects; pCavg= predicted average concentration from Cmin; POS=posaconazole. Note: Adverse Events are presented in decreasing frequency based upon all PK Evaluable Subjects.

Subjects with high exposure versus low exposure

These analyses were focused on the proposed 300-mg dose in an effort to eliminate any bias of the actual dosage administered (200 mg vs. 300 mg) on the safety assessment. Furthermore, in an effort to eliminate any effect of the predicted Cavg (pCavg) calculation on the exposure variable, the analyses were performed by classifying subjects based upon the actual observed steady state Cmin (trough) values rather than predicted Cavg.

Table 14-3 Summary of Adverse Events by Category For PK Evaluable Subjects Number (%) of Subjects Cmin ≤ 2,500 ng/mL vs. > 2,500 ng/mL (Protocol No. P05615)

	POS 300 mg Cmin ≤ 2,500 n=161		POS 300 mg Cmin > 2,500 n=25	
Category				
Treatment Emergent AE	159	(99)	24	(96)
Treatment-Related Treatment Emergent AE	64	(40)	11	(44)
Serious AE	53	(33)	5	(20)
Death	15	(9)	0	
Severe/Life-Threatening Treatment Emergent AE	85	(53)	12	(48)
Study Drug Discontinuation due to AE	21	(13)	3	(12)

Table 14-4 Summary of Adverse Events, by Category For PK Evaluable Subjects Number (%) of Subjects Cmin ≤ 3,750 ng/mL vs. > 3,750 ng/mL (Protocol No. P05615)

	POS 300 mg Cmin ≤ 3,750 n=180		POS 300 mg Cmin > 3,750 n=6	
Category				
Treatment Emergent AE	177	(98)	6	(100)
Treatment-Related Treatment Emergent AE	71	(39)	4	(67)
Serious AE	58	(32)	0	
Death	15	(8)	0	
Severe/Life-Threatening Treatment Emergent AE	94	(52)	3	(50)
Study Drug Discontinuation due to AE	23	(13)	1	(17)

In the Cmin > 3,750 ng/mL subgroup (Table 14-6 and Table 14-8), there were four adverse events that occurred in more than 1 subject; they were events of Hypertension (3 subjects), Alanine Aminotransferase Increased (AST; 2 subjects), Aspartate Aminotransferase Increased (ALT; 2 subjects), and Blood Alkaline Phosphatase Increased (3 subjects). Most of these events were not related to study therapy (often due to extenuating circumstances) and/or resolved with continued posaconazole treatment; see the comment section of Table 14-9 for additional information regarding these AEs.

Post marketing experience

There is no post-marketing experience with Noxafil gastro resistant tablets.

2.6.1. Discussion on clinical safety

The adverse event profile of posaconazole has been established for the oral suspension. Common adverse events include gastrointestinal side effects (diarrhoea and vomiting), abnormal liver function tests, electrolyte abnormalities and hypersensitivity reactions (rash). Hepatotoxicity is usually reversible, but rare cases of fatal hepatotoxicity have been reported. QT prolongation is known to occur and is a class effect of azoles.

The pattern of the most common treatment-related AEs observed in this study was similar to the AEs seen with the oral suspension. The proportion of deaths, SAEs and of patients who had to be discontinued from treatment due to AEs was lower than in studies with the oral suspension in cross study comparisons. However, while exposure levels were higher with the tablet, overall treatment duration and hence cumulative exposure and follow- up was lower than in the studies with the oral suspension. There were also fewer patients with baseline laboratory abnormalities enrolled in this study.

SAEs with at least a possible relationship to treatment were reported in 6 cases in the 300mg group, of which there were 2 cases of renal failure and 2 cases of abnormal liver function test.

Hepatotoxic effects or abnormal lever function tests were reported from 18 patients, in 9 cases these were considered to be drug related. In 5 of these patients treatment was discontinued, and 2 met the criteria for Hy's law. Posaconazole plasma concentrations were reported to be < 2500 ng/ml for all of

the patients considered to have treatment related hepatic events, including those meeting Hy's law's criteria. Two patients with hepatic AE (of mild- moderate severity) considered unrelated had posaconazole plasma concentrations of around 3400ng/ml.

QT prolongation led to drug discontinuation in one case.

A positive association between exposure and overall treatment related AEs was not observed. The number of cases is however too small to draw firm conclusions. A slightly higher incidence of AEs was in fact observed in the first (lowest) quartile. This observation may be an indication that patients with lower exposure are those who are more unwell, leading not only to decreased absorption but also making them more likely to develop adverse events. There was no clear relationship between exposure and the most relevant adverse events, including abnormal liver function tests, although it does appear that compared to the oral suspension, hepatic adverse events were overall somewhat more common. As a limiting factor, it must be stressed that in this population, attributing a specific adverse event to a specific treatment is very challenging indeed.

The frequency of adverse events in patients with exposures above and below 2500mg/ml and above and below 3750ng/ml was compared in the 300mg dose group. Comparisons were based Cmin rather than Cavg. There was no clear increase in overall numbers of adverse events in those with exposures > 2500ng/ml. Hypomagnesaemia and abnormal liver function tests were more frequently observed with higher exposure, but there was no reported increase in grade 3 and 4 changes from baseline for the laboratory abnormalities.

There were only 6 patients with Cmin> 3750ng/ml. Of these, 4 experienced treatment related AEs, three of which were severe and one of which lead to treatment discontinuation (for hypertension). There was 1 subject with moderately increased LFTs, judged to be treatment related but treatment was continued. In 2 other cases increased LFTs were considered unrelated (LFTs improved during continued treatment with posaconazole in one case, in the second case LFTs were elevated on Day 1 of treatment.)

Analysis of exposure by quartile and comparison of high (>2500ng/ml) versus low (< 2500ng/ml) exposure did not show an exposure related increase in overall AEs. There may be a higher number of patients with abnormal liver function tests and hypomagnesaemia, however an increase in higher grade laboratory abnormalities was not reported. The study results therefore do not show an unacceptable increase of overall or specific adverse events with higher exposures. However, the numbers of patients with high exposures (> 2500ng/ml) is small (n= 25), and the observed results have to be interpreted with caution. Most of the common adverse events seen with posaconazole can be monitored in clinical practice. Clear recommendations for monitoring and management of adverse events are included in the SmPC.

2.6.2. Conclusions on the clinical safety

The lack of a control group and shorter duration of treatment makes the interpretation of the adverse events difficult. Based on the data presented, it appears that patients with higher exposures did not experience more or more serious adverse events than those with lower exposures. The number of patients with high exposures is however low.

The majority of adverse events observed with posaconazole can be further monitored.

The safety database particularly where high exposures are concerned is currently small. The applicant was asked to suggest measures to collect further data to increase the safety database and generate further exposure-response data. At present, there is an on-going study PN069 aiming to recruit 600 patients (50% of which will received posaconazole in tablet and or IV form) and investigating the efficacy and safety of posaconazole in the treatment of IFI. The study is expected to generate relevant additional safety data.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan: The RMP is acceptable.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 10, the PRAC considers by consensus that the risk management system for Noxafil in the treatment and prophylaxis of fungal infections (as detailed in section 4.1 of SmPC) is acceptable.

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

- **Safety concerns**

The MAH identifies the following safety concerns

Table 1: Summary of safety concerns

Important identified risks	• *Hepatic - Elevated liver enzymes; Hepatotoxicity; Hepatic failure; Hepatitis* • *Blood – Thrombotic thrombocytopenia purpura; Hemolytic uremic syndrome* • *Cardiac – Torsades de pointes* • *General – Drug interaction*
Important potential risks	• *Blood - Agranulocytosis; Aplastic Anemia* • *Cardiac – QTc prolongation; Heart Failure; Myocardial infarction* • *Psychiatric – Depression; Suicide* • *Endocrine – Adrenal Insufficiency* • *CNS – Convulsion; Cerebral ischemia; Cerebral hemorrhage* • *Respiratory – Pulmonary hemorrhage* • *Vascular – Hypertension; Venous thrombosis; Arterial thrombosis* • *Metabolism – Hypokalemia* • *Neoplasms – Occurrence of any neoplasm/malignancy, especially: Hepatic adenoma; Hepatic neoplasm; Adrenal adenoma; Adrenal neoplasm; Phaeochromocytoma* • *Infections – Fungal infections* • *Visual – Photopsia; Visual brightness; Visual disturbances* • *Injury, Poisoning, and Procedural Complications – Medication Error - Related to potential substitution between different formulations (tablet and oral suspension)*
Important missing information	• *Experience in children*

With the introduction of a new formulation, the possibility of medication errors due to substitution between the different formulations, which could result in under-dosage or over-dosage, has been identified as an important potential risk.

The PRAC Rapporteur agrees that the safety concerns listed by the MAH are appropriate.

- **Pharmacovigilance plans**

With the exception of medication error as described above, review of the posaconazole tablet data indicated no new safety concerns arising with this new formulation. The planned pharmacovigilance actions will remain the same as currently in place for the posaconazole oral suspension.

There are no additional pharmacovigilance activities proposed for posaconazole.

The PRAC Rapporteur, having considered the updated data submitted, was of the opinion that routine pharmacovigilance remains sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures

- **Risk minimisation measures**

The PRAC Rapporteur considered that important safety concerns for posaconazole, including the newly-identified risk of medication error, can be efficiently minimised through routine risk minimisation measures.

The summary table provided in the RMP includes not only risk minimisation measures but also refers to pharmacovigilance. This should be corrected in the next version of the RMP.

Table 3: Summary table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimization Measures	Additional Risk Minimization Measures
	Important Identified Risks	
Hepatobiliary disorders – Elevated Liver Enzymes; Hepatotoxicity; Hepatic Failure; Hepatitis	Routine Pharmacovigilance; Close Monitoring; Event specific follow up questionnaire • Warning in Section 4.4 of the SPC that posaconazole should be used with caution in patients with hepatic insufficiency. • Warning in Section 4.4 of the SPC that patients who develop abnormal liver function tests during therapy should be routinely monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of posaconazole should be considered if clinical signs and symptoms are consistent with the development of liver disease.	None
Coagulopathies/Thormbotic Microangiopathies – Thrombotic thrombocytopenia purpura; Hemolytic uremic syndrome	Routine Pharmacovigilance; Close Monitoring;	None
Cardiac disorders - Torsades de pointes	Routine Pharmacovigilance; Close Monitoring; Event specific follow up questionnaire • Warning in Section 4.4 of the SPC that posaconazole should not be administered with medicinal products that are substrates for CYP3A4 and are known to prolong the QTc interval. • Warning in Section 4.4 of the SPC that posaconazole should be used with caution in patients with pro-arrhythmic conditions. • Warning in Section 4.4 of the SPC that electrolyte	None

	disturbances, especially those involving potassium, magnesium, or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.	
General – Drug Interactions	Routine Pharmacovigilance; Close monitoring; Event specific questionnaire. • Contraindication in Section 4.3 of the SPC for coadministration with ergot alkaloids, CYP3A4 substrates, and HMG-CoA reductase inhibitors. • Warning in Section 4.4 of the SPC that posaconazole is an inhibitor of CYP3A4 and should only be used under specific circumstances during treatment with other medicinal products that are metabolized by CYP3A4 • Warning in Section 4.4 of the SPC that concomitant use of posaconazole with rifamycin, antibacterials, certain anticonvulsants, efavirenz, and cimetidine should be avoided unless the benefit to the patient outweighs the risk.	None
Important Potential Risks		
Blood dyscrasias – Agranulocytosis; Aplastic anemia	Routine Pharmacovigilance; Close Monitoring; Event specific follow up questionnaire	None
Cardiac disorders – QTc prolongation	Routine Pharmacovigilance; Close Monitoring; Event specific follow up questionnaire • Warning in Section 4.4 of the SPC that posaconazole should not be administered with medicinal products that are substrates for CYP3A4 and are known to prolong the QTc interval. • Warning in Section 4.4 of the SPC that posaconazole should be used with caution in patients with pro-arrhythmic conditions.	None

	• Warning in Section 4.4 of the SPC that electrolyte disturbances, especially those involving potassium, magnesium, or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.	
Cardiac disorders –Heart Failure; Myocardial Infarction	Routine Pharmacovigilance; Close Monitoring; Event specific follow up questionnaire	None
Psychiatric disorders – Depression; Suicide	Routine Pharmacovigilance	None
Endocrine disorders – Adrenal Insufficiency	Routine Pharmacovigilance; Close Monitoring; Event specific follow up questionnaire	None
CNS disorders – Convulsion; Cerebral ischemia; Cerebral hemorrhage	Routine Pharmacovigilance; Close Monitoring; Event specific follow up questionnaire	None
Respiratory disorders –Pulmonary hemorrhage	Routine Pharmacovigilance; Close Monitoring	None
Vascular disorders – Arterial thrombosis; Venous thrombosis; Hypertension	Routine Pharmacovigilance; Close Monitoring; Event specific follow up questionnaire	None
Metabolism disorders - Hypokalemia	Routine Pharmacovigilance	None
Neoplasms – Occurrence of any neoplasm/malignancy, especially; Hepatic adenoma; Hepatic neoplasm; Adrenal adenoma; Adrenal neoplasm; Phaeochromocytoma	Routine Pharmacovigilance	None
Infections – Fungal infections	Routine Pharmacovigilance	None
Visual disorders – Photopsia; Visual brightness; Visual disturbances	Routine Pharmacovigilance; Close Monitoring	None
Injury, Poisoning, and Procedural Complications – Medication Error Related to Potential Substitution between Different Formulations of Posaconazole (Tablet and Oral Suspension)	Routine Pharmacovigilance; Dosage Form Design; Product Labeling	None
Important Missing Information		
Experience in Children	Routine Pharmacovigilance	None

The PRAC Rapporteur, having considered the updated data submitted, was of the opinion that the proposed risk minimisation measures remains sufficient to minimise the risks of the product in the proposed indications.

The CHMP endorsed this advice without changes.

In addition, it was noted that the on-going study PN069 is referred to in the RMP. Having agreed that additional exposure-related safety data will be collected part of the on-going study PN069, the CHMP noted that the RMP will be updated accordingly at the next opportunity and part of the on-going line extension to IV procedure.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The proposed gastro-resistant tablet formulation has improved absorption when compared to the currently approved oral suspension in a population of patients with acute myelogenous leukemia (AML), myelodysplastic syndromes (MDS) or after hematopoietic stem cell transplant (HSCT). Compared to the oral suspension, the effect of food on absorption is significantly reduced, which is a distinct advantage in the target population, a proportion of which will not be able to comply with food intake requirements of the oral suspension.

When given as a single daily dose of 300 mg without regard for food, mean posaconazole exposure from the tablet is expected to exceed a Cavg of 500 ng/ml, which is considered to be associated with higher rates of clinical success in the treatment and prophylaxis of IFI.

Uncertainty in the knowledge about the beneficial effects

No controlled, adequately powered clinical efficacy trial was conducted with the new formulation. The development programme was based on an observed exposure-response relationship in clinical trials with the oral suspension and relies on limited data due to low case numbers. The chosen efficacy-related exposure target of more than 500 ng/ml is not a clear cut-off separating failure from success.

Risks

Unfavourable effects

Posaconazole has an established adverse effect profile which includes gastrointestinal side effects (diarrhoea and vomiting), abnormal liver function tests, electrolyte abnormalities and QT prolongation. These effects are seen with both the oral suspension and the tablet.

The study data and model derived simulated data indicate that a relevant proportion of patients will exceed plasma concentrations of 2500 ng/ml and also the upper target limit of 3750 ng/ml. There are limited safety data for these exposure levels, as they were seen to a lesser extent - or not at all - in the studies with the oral suspension.

Uncertainty in the knowledge about the unfavourable effects

The review of the safety data did not show any unexpected adverse events compared to previous studies with the oral posaconazole suspension. However, the value of new safety data generated with the tablet formulation in supporting this application is limited by the lack of a control group. The company provided data to demonstrate that patients with higher exposures do not experience more or more severe adverse events than those with lower exposures, however less than 50 patients were observed with exposures > 2500 ng/ml and only 6 with > 3750 ng/ml. Confounding causality factors for adverse events in the target population contributes to difficulties in data interpretation.

PK and safety data stem from patients with AML and MDS or those after HSCT who received posaconazole for prophylaxis. No data were generated for patients with other underlying diseases and active fungal infections.

It has been established that the gastro-resistant tablet does have a food effect (50% increase in AUC with a high fat meal). This was not taken into consideration in the pivotal trial, where posaconazole was administered without regard for food. This may affect the generalizability of the trial data.

Balance

Benefit-risk balance

Based on the evidence provided, the benefit risk balance for the proposed dose of 300 mg is considered positive for Noxafil gastro-resistant tablets.

Discussion on the benefit-risk assessment

The proposed daily dose of 300 mg is appropriate in a large proportion of patients, but due to the high PK variability some patients may experience unnecessarily high exposures. Extensive explorations and simulations for dose adjustments have been provided. It was hypothesised that a lower dose of 200mg could reduce the proportion of HSCT patients <60 kg exceeding the target range of Cavg. Nevertheless, in view of the relatively small difference, the lack of *confirmed* safety problems from the available database so far, and the practical difficulties separating subpopulations explained earlier it seems preferable to recommend the 300 mg dose to the whole target population.

The omission of recording the food effect in the pivotal study remains a flaw in the development programme of the tablet formulation, and the CHMP recommended that further information on food intake as well as plasma concentrations over time and when possible plasma concentrations at the time of adverse events should be obtained in the on-going PN069 trial.

Overall, the CHMP was of the opinion that the improved absorption and higher exposure provided by the proposed gastro- resistant tablet, with the implied beneficial effect for efficacy, outweighed the risk of higher exposure in a proportion of patients. This conclusion takes into account that further

efficacy and in particular safety data are generated in the on-going clinical trial in the treatment of IFI with posaconazole.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Noxafil 100 mg gastro-resistant tablet in the treatment of the following 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.

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products on “restricted” medical prescription, reserved for use in certain specialised areas (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.