EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 July 2014
EMA/CHMP/75051/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Noxafil

International non-proprietary name: POSACONAZOLE

Procedure No. EMEA/H/C/000610/X/0033

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Product information

Name of the medicinal product	Noxafil
Applicant:	Merck Sharp & Dohme Limited Hertford Road Hoddesdon EN11 9BU UNITED KINGDOM
Active substance:	Posaconazole
International nonproprietary name/common name:	Posaconazole
Pharmaco-therapeutic group (ATC code):	Anti-infectives for systemic use, triazole derivatives. (J02AC04)
Therapeutic indication(s):	Noxafil is indicated for use in the treatment of the following fungal infections in adults: - 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.
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	18 mg/ml (each vial contains 300mg of posaconazole)
Route(s) of administration:	Intravenous use
Packaging:	Type I glass

Table of contents

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Merck Sharp & Dohme Limited submitted on 02 September 2013 an application for an extension of Marketing Authorisation to the European Medicines Agency (EMA) for Noxafil 18 mg/ml concentrate for solution for infusion, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2, indents d and e) of the Commission Regulation (EC) No 1234/2008.

Merck Sharp & Dohme Limited is the Marketing Authorisation Holder for Noxafil 40 mg/ml oral suspension (EU/1/05/320/001) and Noxafil 100 mg gastro-resistant tablet (EU/1/05/320/002 and 3).

The applicant applied for the following indication: Noxafil is indicated for use in the treatment of the following fungal infections in adults:

- 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.

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:

Scientific advice was obtained for the intravenous formulation and this advice has been taken into account for the development of the new proposed formulation (ref. EMA/CHMP/SAWP/434090/2010, Procedure No.: EMEA/H/SA/233/2/FU/2010/III). The Advice from CHMP concerned the exposure response data supporting dose selection for posaconazole intravenous (IV) formulation development program based on achieving a steady state target Cavg between 500 and 2500 ng/mL, previously proven to be efficacious and safe for both treatment and prophylaxis. This was received in a Follow-up Scientific Advice procedure which was finalized 22 July 2010.

Licensing status:

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

1.2. Manufacturing authorisation holder

Manufacturer(s) responsible for batch release

Schering-Plough (Brinny) Company

Brinny, Innishannon

Cork

Ireland

Schering-Plough Labo N.V.

Industriepark 30

Heist-op-den-Berg - Zone A

BE-2220 Antwerpen

Belgium

Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Dr. R. Suvarna

- The application was received by the EMA on 02 September 2013.
- The procedure started on 25 September 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 December 2013
- During the PRAC meeting on 9 January 2014, the PRAC adopted an RMP Advice and assessment overview
- During the meeting on 20-23 January 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 23 January 2014
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 March 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 April 2014.
- During the PRAC meeting on 8 May 2014, the PRAC adopted an RMP Advice and assessment overview
- During the CHMP meeting on 19-22 May 2014, 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 19 June 2014.
- The Rapporteur circulated the joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 2 July 2014
- During the PRAC meeting on 10 July 2014, the PRAC adopted an RMP Advice and assessment overview
- During the meeting on 21-24 July 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 18 mg/ml concentrate for solution for infusion.

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 or, recently, as a gastro-resistant tablet (Noxafil).

An intravenous (IV) formulation for high-risk subjects who experience periods of inability to take oral medication is considered to be useful in this population.

In this application, the Applicant is seeking to add an additional dosage form (concentrate for solution for infusion) and route of administration (intravenous) of posaconazole. This new presentation is formulated as an aqueous injectable solution containing 18 mg/mL of posaconazole for the same indications currently approved for the oral suspension (with the exception of treatment for oropharyngeal candidiasis) and gastro-resistant tablet.

2.2. Quality aspects

2.2.1. Introduction

The finished product is available as 18 mg/ml concentrate for solution for infusion of posaconazole as active substance.

Other ingredients are: betadex sulfobutyl ether, edetate disodium, hydrochloride acid, sodium hydroxide and water for injections.

The product is available in 20 ml glass vial (type I) with bromobutyl Omniflexplus coated rubber stoppers and an aluminium flip-off seal as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The active substance used in Noxafil 18 mg/ml concentrate for solution for infusion, is the same active substance as the one approved for the currently authorised Noxafil 40 mg/ml Oral suspension. The assessment of the active substance was conducted as part of the initial application (EU/1/05/320/001). Therefore, Module 3.2.S has not been re-submitted, but confirmation that no changes or updates have been made to the ASMF has been provided by the applicant.

2.2.3. Medicinal Product

Description of the product and pharmaceutical development

The objective of the pharmaceutical development was to produce a stable concentrate for solution for infusion suitable for intravenous administration. The pharmaceutical development contains Quality by Design (QbD) elements, such as risk assessment, PAT models. The quality target product profile (QTPP)

and Critical Quality Attributes (CQAs) were defined, discussed and considered acceptable. Nevertheless, it is important to underline that the applicant did not apply for a design space for the manufacturing process of the finished product.

Early steps of the formulation design were focussed on selection of a solubilising agent and various formulations manufactured using various combinations of solutol, PEG, ethanol, sodium edetate, lactic acid, hydroxypropyl-β-cyclodextrin (HPBCD), and betadex sulfobutyl ether at posaconazole concentrations of 5-20 mg/ml. The formulation selected for development was 20 mg/ml posaconazole formulated with betadex sulfobutyl ether (400 mg/ml), and sodium edetate (0.1 mg/ml), diluted 10 fold with normal saline prior to infusion.

The solubility of posaconazole at various pH values was evaluated by adding an excess of posaconazole to solutions of betadex sulfobutyl. The solubility was highest at pH 2 and the relationship between betadex sulfobutyl concentration and posaconazole solubility is non-linear at pH 3 and 4.5.

The potential for posaconazole solubility improvement using acidifiers, co-solvents and non-ionic surfactants was evaluated using 17 compounds. Saturation solubility data was described and no significant improvement observed with any excipient. Hydrochloric acid was selected as a pH adjuster on the basis of its wide use for pharmaceutical products and no co-solvent or surfactant was proposed.

The final concentrations of posaconazole and betadex sulfobutyl ether were 18 mg/ml and 400 mg/ml respectively. A pH value of 2.6 was selected to maintain posaconazole solubility between approximately 24-34 mg/ml.

A concentration of 1.0 mg/ml EDTA and nitrogen sparging during manufacture were selected.

All 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.

Extensive screening studies were performed to select the appropriate pH, excipients and concentrations required to solubilize and stabilize the active substance in the commercial formulation. Multiple solubilizers and acidifiers were investigated prior to the selection of the ones used in the commercial formulation. The final formulation was selected as having the most suitable solubility, stability and compatibility of the excipients with the active substance. A concentration of 1.0 mg/ml EDTA and nitrogen sparging during manufacture were selected.

The formulation, used in the clinical studies is identical to the proposed commercial product. The formulation of posaconazole concentrate for solution for infusion remains unchanged during the clinical development batches and the batches used for Primary Stability Studies (PSS) and the proposed commercial presentation.

The primary packaging is described as stated in the SmPC. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data. This container was selected on the basis of compatibility and container-closure integrity studies and is adequate for the intended use of the medicinal product.

Manufacture of the product and process control

The manufacturing process consists of the following main steps: mixing, filtration, solution acidification, pH adjustment, sterilising filtration, aseptic filling, capping and packaging. Satisfactory flow-chart with in-process controls of the manufacturing process including tests such as appearance, dissolution of the excipients, pH, filter integrity and fill weight have been included.

Depyrogenation of the vials and stoppers is performed in a dry heat tunnel and manufacturing equipment is sterilised by steam sterilisation using an autoclave. The vial sterilisation step was adequately validated for different temperatures. The filling step stoppering parts are also sterilised by dry heat and the process was adequately validated.

The validation of the manufacturing process was conducted on three consecutive production scale batches and by appropriate media fills studies. The quality of the production batches was evaluated through the results of in-process testing as well as the results of finished product testing. The validation protocol was enclosed in the dossier and it was considered satisfactory.

Product specification

The finished product release specifications include appropriate tests for this kind of pharmaceutical form: appearance (visual), colour (visual), identification (HPLC and UV), assay (HPLC), impurities (HPLC), pH (Ph Eur), particulate contamination (Ph Eur), extractable volume (Ph Eur), bacterial endotoxins (Ph Eur) and sterility (Ph Eur).

Batch analysis data of 17 batches of different scales of the finished product are provided. The results confirm the consistency of the process and its ability to manufacture a product complying with the product specification.

Stability of the product

Stability data of seven pilot and five commercial scale batches of finished product stored under long term conditions for thirty six months at 5 ºC ± 3 ºC, up to nine months under accelerated conditions at 25 ºC / 60% RH and up to six months under accelerated conditions at 30 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The analytical methods used were the same as for release and were stability indicating.

One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The data demonstrate that the medicinal product is not affected by light.

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

Adventitious agents

No excipients derived from animal or human origin have been used, but a statement of compliance with the TSE/BSE requirements has been provided by the betadex sulfobutyl ether manufacturer, as this is manufactured by fermentation using bovine casein.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product for this new presentation 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 clinical use. The applicant has applied QbD principles in the development of the finished product. However, no design spaces were claimed for the manufacturing process of the finished product.

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. Recommendations for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

This application is supported by the non-clinical safety programme conducted for the currently authorised Noxafil oral suspension, as well as the safety pharmacology, pharmacokinetic and toxicology studies conducted in support of a previous IV suspension formulation that was discontinued.

2.3.2. Pharmacology

Not applicable

2.3.3. Pharmacokinetics

The pharmacokinetics of posaconazole has previously been presented by the Applicant in the initial MA dossier. In the new submitted studies, three additional non-clinical studies (a 28-day toxicity study in Cynomolgus monkeys and two local tolerance studies in rats) in support of the POS IV application were submitted in order to determine plasma concentrations for comparison to the POS oral toxicity programme.

2.3.4. Toxicology

There were no single dose toxicity, genotoxicity or carcinogenicity studies conducted. This is acceptable in view of the previously submitted data.

To demonstrate that no new toxicities occurred with POS IV Solution, two pivotal studies, a 1-month study in young adult monkeys and a 3-month study in young adult dogs were conducted. Toxicokinetic data were collected to support these studies and determine plasma concentrations for comparison to the POS oral toxicity programme.

A non-dose related low incidence of thrombus/embolus in the lung were observed in the 28-day monkey study in animals in the POS IV Solution dose groups. This finding occurred in 1 male and 1 female at 4mg/kg, 2 males at 8mg/kg and 1female at 12mg/kg (low-, mid-, and top dose respectively). Although this finding was not seen in controls, because of the low incidence in dosed animals and the lack of a dose response, the applicant proposed that the presence of a thrombus/embolus in the lung was procedure-related. The pulmonary thrombus/embolus were attributed to irritation at the catheter tip and subsequent migration of thrombi from the catheter tip to the lungs, a finding consistent with IV infusion studies using surgically-implanted indwelling catheter. Catheter site findings following administration of

POS IV Solution via femoral vein catheter with the tip in the inferior vena cava were observed in all groups and were consistent with irritation and occurred at a similar frequency and severity across all dose groups, including controls, and were considered procedure related. The fact that the finding was reported only in the treated animals indicates the finding could be treatment related. The applicant was requested to discuss the mechanism for, and the clinical significance of, the thrombo-embolic events reported in this study. An explanation for the occurrence of the thrombo-embolic events reported in the monkey 28-day study has been submitted. The data provide some support for the hypothesis that the emboli were caused by the occurrence of clots forming at the tip of indwelling catheters, which could migrate and become lodged in the lung. However, the CHMP noted some concerns about infusion site reactions and thrombophlebitis and the potential for thromboembolic events (see also section 3.6 Clinical Safety).

Toxicokinetics in this study revealed greater than proportional systemic exposure following repeated administration. The applicant was requested to discuss the mechanism and clinical significance of this finding. A plausible explanation is that it may be due to a saturation of elimination, as indicated by the decreased clearance and accompanying increase in half life with dose. The clinical significance is minimal given the dose-proportional increase in exposure in the clinically relevant dose range of 200-300 mg IV.

POS IV Solution was also evaluated in juvenile dogs. Only one dose (10 mg/kg) was used. The rationale for this study design is not clear. The applicant stated that the purpose of this study was to assess the safety of a low dose of the test item when administered via the intravenous route during juvenile development based on treatment related findings at 60 mg/kg in a previous oral dose study in juvenile animals. However, since the dose of the current study was significantly lower due to formulation constraints, it was unclear whether these findings would occur. Well-characterized POS toxicities (the same as those seen in adult animals) were observed in this study. In addition, enlargement of the lateral ventricles in the brain was observed. At the end of the dosing period (main study), dilatation of the lateral ventricles of the brain was observed grossly and histologically in 2/4 females and 3/4 males in the 10 mg/kg POS group. The applicant considered that these changes were most likely treatment related based upon the high incidence relative to concurrent or historical control animals and the fact that the change was observed in pups from 2 different, genetically unrelated dams. No difference in the incidence of brain ventricle enlargement between control and treated animals was observed following the subsequent 5-month treatment-free period. There were no neurological or behavioural abnormalities in the dogs with this finding. The finding of brain ventricular dilation in juvenile dogs after 6 weeks of POS IV Solution administration (where animals were dosed from post-natal Day 14 to postnatal Day 56) is claimed by the applicant to cover the period of development equivalent to a human age of 3 months to approximately two years of age. These juvenile brain ventricular dilation findings were not observed in adult dogs administered POS IV Solution for three months where similar or higher POS exposures were attained relative to the juvenile studies. In addition, a suspension formulation of POS (not further developed for clinical application) was intravenously administered to young adult rats and young adult monkeys for three month durations and was without brain ventricular dilation findings; POS systemic exposures were similar or exceeded those achieved in the juvenile dog study testing POS IV solution. The applicant hypothesised that observation of brain ventricular dilation following POS IV Solution administration in juvenile dogs, but not following POS IV Solution administration in adult dogs and monkeys, or following POS IV Suspension administration to adult rats and monkeys, suggests that potential interference to brain ventricle development may account for findings in the juvenile dog studies with POS IV Solution. Brain ventricular development in humans is understood to be completed well prior to 18 years of age, and therefore the applicant considers that this potential risk is not relevant to adults (persons aged 18 years or older). In fact, the clinical significance of this finding is unknown, although the fact that the finding was reported in one study only provides reassurance. It is also noted that this finding is included in section 5.3 of the Noxafil SmPC and that the use of posaconazole in patients under 18 years of age is not recommended.

The applicant conducted a three-month intravenous infusion toxicity study in dogs (TT #13-1062). This study was conducted in compliance with GLP, with the exception that the MRI scans and analysis of drug concentrations in cerebral spinal fluid and brain samples were performed using a non-GLP assay. The dose level selected was stated to be based on the results from previous studies. However these studies were not specified. The objectives of this study were to determine the potential toxicity and toxicokinetic profile of Posaconazole, when administered as a daily 15-minute intravenous infusion to dogs for approximately 3 months. Four female and 4 male beagle dogs received 9 mg/kg/day of posaconazole formulated in a vehicle of 5% Dextrose. The dose was delivered as a 15-minute intravenous infusion. The dosing volume was 5 mL/kg. A control group of 4 female and 4 male dogs received the vehicle only. Dogs were 31 to 35 weeks old at study start. Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, gross examination, organ weight of brain, and histological examination of the brain. Drug concentrations in the plasma in the treated and control samples were determined. In addition, exploratory measurement of drug concentration in the cerebral spinal fluid (CSF), and brain samples from all groups were conducted. Exploratory Magnetic Resonance Imaging (MRI) examinations were conducted pre-test, and study weeks 3, 7 and 12-13 on the brain to evaluate the brain ventricle volumes.

All animals survived to scheduled sacrifice. There were no treatment related overt signs of toxicity or effects on body weight or food consumption. There were multiple pale foci on the lungs of 7/8 dogs treated with posaconazole which were considered likely due to phospholipidosis. Phospholipidosis has been observed grossly and histologically in lungs of dogs as a test article-related finding in previous pre-clinical studies. There were no test article-related changes in brain weights or histological findings in the brain. The ventricles of the brain in treated dogs were similar to control dogs when evaluated by gross observation during trimming of the fixed brain and by histomorphology. There were no test article-related changes in brain ventricle volumes as determined by MRI. No significant differences in brain ventricle volume were seen between groups.

Systemic exposure to posaconazole was independent of sex. Following repeated administration, systemic exposure to posaconazole increased in Study Week 7 compared to Study Day 1. Mean AUC0-24 hr and Cmax values in Study Week 7 were approximately 3.1- and 2.2-fold higher than on Study Day 1, respectively.

The main concern in this study was the increase in brain ventricle volume in both the treated and vehicle groups. The statistical analysis was not informative. The largest increase was in the vehicle control group indicating that the increase is not treatment related.

Assessment of the local irritation potential of POS IV Solution showed that it was well tolerated and behaved similarly to controls. Exposure multiples for the IV solution were similar to those achieved with POS oral administration.

Reproductive and developmental toxicity studies were performed with oral administration of POS to support the use of the oral suspension. IV bridging studies in the rat and rabbit demonstrated similar POS exposure profiles via oral and IV routes. There was no fertility and early embryonic development, embryo-foetal development or pre- and post-natal developmental toxicity studies conducted with POS IV Solution.

2.3.5. Ecotoxicity / environmental risk assessment

Based on a Phase I assessment, the Predicted Environment Concentration (PEC) for posaconazole exceeded the trigger for requiring an environmental assessment. Therefore a Phase II-Tier A environmental effect assessment and concomitant risk assessment was conducted. Based on the log Kow

of 4.15, a further Persistence, Bioaccumulation and Toxicity (PBT) screening was not warranted. However, the applicant was requested to clarify the PEC/PNEC ratio used and the maximum daily dose for this application. A satisfactory response has been submitted. The transformation products of posaconazole are persistent in a water-sediment system. The active ingredient posaconazole is persistent in the environment.

Based on the Phase II–Tier A assessment, posaconazole is unlikely to represent a risk to surface water, ground water micro-organisms and sediment dwelling organisms. Posaconazole is not likely to bioconcentrate in aquatic organisms and is not a PBT compound (BCF < 2000), indicating little risk to the aquatic and sediment environments. The applicant was requested to provide information on the recalculated half-lives of the parent and transformation products in sediment. A satisfactory response has been submitted. No further action is necessary and no special precautions need to be taken for the disposal of posaconazole.

2.3.6. Discussion on the non-clinical aspects

The submission of POS IV Solution was supported by the non-clinical programme conducted for the already marketed POS Oral Suspension, as well as safety pharmacology, pharmacokinetic and toxicology studies conducted in support of POS IV Suspension, a previous IV formulation that was discontinued.

The objective of the non-clinical toxicology programme for POS IV Solution was to identify any new toxicities specific to this IV formulation. Thus, the non-clinical toxicology programme for POS IV Solution consisted of two pivotal studies, a completed 1-month study in young adult monkeys and a 3-month study in young adult dogs to bridge to the existing non-clinical experience with POS. A study in juvenile dogs was also conducted. In addition, two single-dose studies in rabbits (one local tolerance study and one IV infusion tolerance study) were conducted to evaluate the irritation potential of this formulation.

An Environmental Risk Assessment (ERA) which included a number of new studies has also been submitted.

In the 6-week juvenile dog study, in addition to the well characterised POS toxicities, enlargement of the lateral ventricles in the brain was observed. There were no neurological or behavioural abnormalities in the dogs with this finding. These findings were not observed in adult dogs administered POS IV Solution for three months where similar or higher POS exposures were attained relative to the juvenile studies. In addition, a suspension formulation of POS (not further developed for clinical application) was intravenously administered to young adult rats and young adult monkeys for three month durations and was without brain ventricular dilation findings; POS systemic exposures were similar or exceeded those achieved in the juvenile dog study testing POS IV solution. The applicant hypothesised that observation of brain ventricular dilation following POS IV Solution administration in juvenile dogs, but not in other studies, suggests that potential interference to brain ventricle development may account for findings in the juvenile dog studies with POS IV Solution. The clinical significance of this finding is unknown, although the fact that the finding was reported in only one study provides reassurance. This finding is included in section 5.3 of the SmPC and the use of posaconazole in patients under 18 years of age is not recommended.

A non-dose related low incidence of thrombus/embolus in the lung were observed in the 1-month monkey study in animals in the POS IV Solution dose groups. Although this finding was not seen in controls, because of the low incidence in dosed animals and the lack of a dose response, the applicant proposed that the presence of a thrombus/embolus in the lung was procedure-related. The pulmonary thrombus/embolus were attributed to irritation at the catheter tip and subsequent migration of thrombi from the catheter tip to the lungs, a finding consistent with IV infusion studies using surgically-implanted

indwelling catheter. However, the fact that the finding was reported only in the treated animals indicates the finding could be treatment related. The applicant submitted data which provide some support for the hypothesis that the emboli were caused by the occurrence of clots forming at the tip of indwelling catheters, which could migrate and become lodged in the lung. However, the CHMP noted some concerns about infusion site reactions and thrombophlebitis and the potential for thromboembolic events (see also section 3.6 Clinical Safety).

Assessment of the local irritation potential of POS IV Solution showed that it was well tolerated and behaved similarly to controls. Exposure multiples for the IV solution were similar to those achieved with POS oral administration. At the clinical IV dose of 300 mg QD, steady state exposure to POS in subjects at high risk for invasive fungal infections was similar to or less than the exposure obtained in the non-clinical toxicity studies that supported the oral suspension registration and in the toxicity studies with the IV solution.

An ERA revealed that posaconazole is unlikely to be a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data and discussion provided in this submission adequately support this application. There are no major objections and all the other concerns have been fully resolved, with some remaining concerns about infusion site reactions and the potential for thromboembolic events also discussed and assessed in section 3.6 Clinical Safety.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

- **Development rationale**

Noxafil was developed initially as an oral suspension. Posaconazole (POS) oral suspension is very poorly soluble in water, has to be administered 2 to 4 times a day and has to be taken with food (preferably a high fat meal) or nutritional supplement to ensure adequate exposure among patients. A gastro-resistant tablet, with a reduced food effect and providing overall higher exposure than the equivalent dose of POS oral suspension, has recently been approved (X-028, CHMP opinion adopted on 20 February 2014). An intravenous (IV) formulation for high-risk subjects who experience periods of inability to take oral medication is considered useful in this population. The applicant is seeking approval of an IV form of posaconazole, a posaconazole concentrate for solution for infusion (hereafter referred to as POS IV solution), an aqueous injectable solution containing 18 mg/mL of posaconazole for the same indications currently approved for the oral suspension (with the exception of treatment for oropharyngeal candidiasis). The clinical development program for the POS IV solution was designed to bridge to the prior POS oral suspension clinical program. The new IV formulation is an aqueous solution containing the solubilizer sulfobutylether beta-cyclodextrin (SBEβCD), which is the same solubilizer used in the IV formulation of another azole antifungal, voriconazole.

- **Bridging strategy**

The clinical program for IV POS solution has been designed to demonstrate comparable exposure and safety for the intravenous formulation of posaconazole among the same patient populations for which the POS oral suspension has already been approved. To this end, the primary intent of the pivotal clinical study in patients (P05520) was to fully characterize the pharmacokinetics (PK) and assess safety of IV POS solution in neutropenic subjects (AML and MDS) and 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 POS-treated subjects than in control subjects when POS 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)

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

Table 1.

		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 POS oral suspension at the approved clinical dose have been used by the applicant 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 POS plasma concentration following POS oral suspension was 583 ng/mL, with 90% of patients attaining POS average plasma levels (Cavg) greater than or equal to 228 ng/mL. In study C/I98-316, the mean POS plasma concentration following POS oral suspension was 1130 ng/mL with 90% attaining POS plasma Cavg greater than or equal to 322 ng/mL.

Further, in study P000041 (treatment of IFI), in the lowest quartile exposure was only 134 ng/mL with a corresponding clinical response to therapy of 24%, and patients in the 4th quartile, who had a steady-state Cavg mean value of 1250 ng/mL, had a 71% response rate at EOT. The Cavg of 1250 ng/mL translates to a steady-state area under the plasma concentration versus time curve from time 0 to 24 hours (AUC[0-24 hr]) of approximately 30,000 ng*hr/mL. Based on this, a Cavg value of approximately 1200 ng/mL was selected as the target exposure for IV POS solution.

The primary intent of the pivotal clinical study in high-risk subjects (P05520) was to fully characterize the pharmacokinetics (PK) and assess safety of POS IV solution in neutropenic subjects (AML and MDS) and

subjects who had undergone an HSCT and were under treatment for GvHD. This Phase 1b/3 study was designed as the bridging study to the prior POS oral suspension clinical program. An exposure range for POS IV solution was targeted that had been previously shown to be efficacious and safe with the POS oral suspension clinical development program in the prophylaxis and salvage treatment setting.

The exposure target range for the use of POS IV solution in subjects was set as below:

Mean steady-state Cavg of around 1,200 ng/mL (or AUC[0-24] of 28,800 ng.hr/mL) with at least 90% of the subjects between 500 ng/mL (or AUC[0-24] of 12,000 ng.hr/mL) and 2,500 ng/mL (or AUC[0-24] of 60,000 ng.hr/mL); and

• No subject with mean Cavg at steady-state above 3,650 ng/mL (or AUC[0-24] above 87,600 ng.hr/mL); and

• No subject with mean Cavg at steady-state below 200 ng/mL (or AUC[0-24] below 4,800 ng.hr/mL).

Cavg was the exposure parameter used in studies with POS 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.

2.4.2. Pharmacokinetics

Earlier studies have characterized the pharmacokinetic (PK) and toxicologic profile of POS oral suspension. POS oral suspension is slowly absorbed, extensively distributed into the tissues, and slowly eliminated, without any major circulating metabolites. Of the circulating metabolites, the majority are glucuronic acid conjugates of POS with only low levels of oxidative metabolites. Exposure of POS oral suspension can be increased by dividing the POS 800 mg/day dose to BID or QID and administering the dose with food. The pharmacokinetics of POS oral suspension are not significantly altered in subjects with hepatic or renal dysfunction or in subjects who differ by age, race, gender or weight. POS is an inhibitor of CYP3A4 at clinically relevant concentrations. The clinical development program for POS IV solution was designed to bridge to the prior POS oral suspension clinical program.

- **Analytical Methods**

The analytical methods used for quantification of POS in human plasma were validated for specificity, sensitivity, and reproducibility. The bioanalytical methods utilized were based on a solid phase extraction of the analytes from the biological matrix followed by liquid chromatography (LC) coupled with tandem mass spectrometric detection (MS/MS).

2.4.2.1. Individual Clinical Pharmacology Studies

There are three (3) healthy volunteer studies and one (1) study in high risk subjects with POS concentrate for solution for infusion.

Table 2.

Study	Short Protocol Titles	Study Design/ Population	Dose Levels Administered (mg)	Administration IV	Number of Subjects Treated	PK parameters
P04985	PK, safety & tolerability study in healthy volunteers (SD and MD)	XO Healthy volunteers	SD: 200	Peripheral infusion over 90 minutes	Active (IV POS): 9 Placebo: 3	Single dose C_{max}, $AUC_{0-\infty}$, AUC_{tf}
P06356	PK, safety & tolerability study in healthy volunteers (SD and MD)	Fixed sequence Healthy volunteers	SD: 0 (vehicle IV solution only), 50, 100, 200, 250, and 300 MD: 100 bid on Day 1, QD on Days 2-10	Peripheral infusion over 30 minutes	SD: Active (IV POS): 45 Captisol® (cyclodextrin vehicle only): 9 Placebo (D5W): 18 MD: Active (IV POS): 5* Captisol® (cyclodextrin vehicle only): 9* Placebo (D5W): 4*	Single dose C_{max}, $AUC_{0-\infty}$, AUC_{tf} Multiple dose AUC. , C_{avg} and C_{max}
P07783	Absolute bioavailability and MD PK study in healthy volunteers (SD and MD)	XO Healthy volunteers	SD: 300	Peripheral infusion over 30 minutes	Active (POS): 13	Single dose Cmax, AUC0-∞, AUCtf
P05520	PK, safety & tolerability study in high risk subjects; IV solution followed by oral suspension	Parallel group High risk subjects	**Cohort 0:** 200 (SD) or placebo **Cohort 1 and 2:** 200 and 300 mg BID on Day 1, followed by 200 mg or 300 mg QD on Days 2-14 **Cohort 3:** 300 mg BID on Day 1 followed by 300 mg QD for a minimum of 5 days All cohorts: step down to POS oral suspension	Central line infusion of POS IV solution for 1 day (Cohort 0), 14 days (Cohorts 1 and 2), or at least 5 days (Cohort 3), followed by POS oral suspension 400 mg BID (Cohorts 0-3) or 200 mg TID (Cohort 3 only)	**Cohort 0**: Active (POS): 10 Placebo (D5W): 11 **Cohort 1**: POS 200 mg: 21 **Cohort 2**: POS 300 mg: 24 **Cohort 3**: POS 300 mg: 213	Multiple dose AUC_T, C_{avg} and C_{max}

XO = crossover; SD = single dose; MD = multiple dose; POS= posaconazole; D5W= 5 % dextrose in water

* Eight and 2 subjects completed the treatment Phase in the Captisol® and Placebo groups, respectively. All subjects on active treatment were discontinued on Days 2-4.

- **Studies in healthy volunteers**

Study P04975

Study P04985 was a randomized, open label, placebo-controlled, rising single and multiple dose, single site phase 1 study. Approximately 24 healthy male and female adult subjects (between 18 and 65 years of age) with a BMI of 19 to 35 were planned to be enrolled in two cohorts.

The primary objective was to evaluate the PK of POS IV solution when administered as single and multiple doses via peripheral infusion over ninety (90) minutes in healthy volunteers.

In Cohort 1, 12 subjects were to be randomized to receive POS IV Solution 200 mg QD/BID (Treatment A) or placebo (9 active/3 placebo). It was planned that 12 different subjects in Cohort 2 would receive POS IV Solution 400 mg QD/BID (Treatment B) or placebo (9 active/3 placebo) followed later by further doses of oral POS. However, the study was terminated early due to local peripheral venous intolerance reactions observed following single-dose infusion of POS IV 200 mg in Cohort 1, Treatment A. Further treatments were not administered.

Table 3. Mean (±SD) POS Plasma Concentration-Time Profiles Following Single Dose Administration of 200 mg POS IV Solution to Healthy Adult Volunteers (P04985)

Title of Study:	An Evaluation of the Pharmacokinetics and Safety of Posaconazole (SCH 56592) IV Solution in Healthy Volunteers (Protocol No. P04985)						
Occurrence of Adverse Events and Injection Site Reactions in Relation to Individual Pharmacokinetic Parameters of POS Following Single Dose, Intravenously administered, 200 mg IV Solution of POS to Healthy Adult Volunteers (**Sorted by AUC∞**)							
Treatment	Subject	Cmax (ng/mL)	Tmax (hr)	**AUC∞ (hr*ng/mL)**	Injection Site Reaction	Extra-vasation	Liver Function Test Abnormalities
POS 200 mg IV Solution (Treatment A: n=9)	102	1500	1	21700	no	no	no
	101	1590	1	22300	no	no	no
	108	1430	1	24600	yes	no	no
	111	1180	1	25300	yes	no	no
	109	691	4	26400	yes	yes	yes
	105	1850	1	26800	no	no	no
	107	1620	1	27200	yes	no	no
	104	1650	1	32900	yes	no	no
	110	1710	1.52	45600	yes	no	no
	n	9	9	9	6 of 9	1 of 9	1 of 9
	Mean	1470	1.39	28100			
	SD	347	0.993	7340			
	Min	691	1	21700			
	Median	1590	1	26400			
	Max	1850	4	45600			
	CV%	24	71	26			
	Geometric Mean	1420	1.22	27400			
AUC∞ =area under the plasma concentration-time curve from time 0-infinity; Cmax=maximum observed plasma concentration; CV=Coefficient of Variation; n=number of subjects; IV=intravenous; Max=maximum; Min=minimum; POS=posaconazole; SD=Standard Deviation; Tmax = time to Cmax.							

- After single dose infusion of 200 mg POS IV solution, infused over 90 minutes, a mean Cmax of 1470 ng/mL (CV%=24%) was attained at a median Tmax of 1 hour.
- The mean AUCinf was 28100 ng·hr·mL-1 (CV%=26%). The mean systemic clearance (CL) of POS was 7.46 L/hr (CV%=20%) and the mean half-life was 24 hours.

Study P06356

This was a randomized, 2-part, third-party blind, placebo-controlled, rising single and multiple dose study, performed at a single site to evaluate the safety, tolerability, and pharmacokinetics of posaconazole IV solution in healthy male and female volunteers 18 to 65 years of age.

After overnight fasting, a total of 72 subjects were randomized in 1 of the 6 cohorts of 12 subjects each (9 active and 3 placebo) and received a peripheral IV solution with vehicle IV solution (without posaconazole, Cohort 1 only) or posaconazole IV solution (Cohorts 2 - 6) or placebo (D5W). The dosing range of posaconazole was 0 (vehicle IV solution only), 50, 100, 200, 250, and 300 mg. In each subgroup, 3 subjects received the vehicle IV solution (Cohort 1 only) or posaconazole IV solution (Cohorts 2 - 6) and 1 subject received the placebo (D5W).

In part 2, a total of 48 subjects were to be randomised to receive multiple doses of IV POS (ranging from 100- 300mg) or placebo. Due to cases of thrombophlebitis in Part 2, the multiple-dose component of this study was discontinued and the single-dose component of the study was amended to test the 250 mg and 300 mg dose levels, instead of the 300 mg and 400 mg dose levels. In addition, to minimize the risk of

thrombophlebitis, it was determined that after completion of the 30-minute SD infusion, the infusion site should be immediately flushed with 20 mL of 5% dextrose for injection (D5W) by IV push.

Results

Table 4. Posaconazole Arithmetic Mean (%CV) Pharmacokinetic Parameters Following IV Single-Dose Administration of 50 - 300 mg Posaconazole to Healthy Volunteers

Dose (mg)	Cohort	n	λz (hr)	t½ (hr)	tmax[a] (hr)	Cmax (ng/mL)	AUC0-last (ng·hr/mL)	AUC0-∞ (ng·hr/mL)	AUC%	Vz (L)	CL (L/hr)
50	2	9	0.0410 (34)	18.7 (34)	0.6 (0.5-0.7)	313 (30)	4620 (31)	4890 (30)	5.95 (62)	294 (39)	10.9 (25)
100	3	9	0.0360 (14)	19.6 (16)	0.5 (0.5-0.5)	1330 (27)	10800 (27)	11200 (26)	4.47 (47)	262 (22)	9.40 (23)
200	4	9	0.0307 (23)	23.6 (23)	0.5 (0.5-24)[b]	2250 (29)	34600 (52)	35400 (50)	2.75 (97)	226 (38)	6.54 (32)
250	5	9	0.0279 (21)	26.0 (23)	0.5 (0.5-0.5)	2260 (26)	40600 (39)	41500 (41)	1.84 (85)	245 (33)	6.68 (29)
300	6	9	0.0292 (20)	24.6 (20)	0.5 (0.5-1.0)	2840 (30)	45500 (26)	46400 (26)	1.74 (46)	236 (17)	6.90 (27)

(a) Median (range); Infusion time = 30 min
(b) One subject had a high concentration at the 24 hr sample; therefore, the tmax is 24 hr for that subject

Table 5. Dose Proportionality Assessment of Posaconazole Following Intravenous Administration of a Single Dose of Posaconazole Ranging from 50 - 300 mg

Parameter	Slope	90% CI		Dose Range	Estimate	90% CI	
		Lower	Upper		fold increase	Lower	Upper
Cmax	1.159	1.018	1.300	50 - 300 mg (6 fold)	7.979	6.197	10.27
AUC0-last	1.328	1.215	1.441		10.80	8.824	13.21
AUC0-∞	1.302	1.191	1.414		10.32	8.452	12.59

Figure 1.

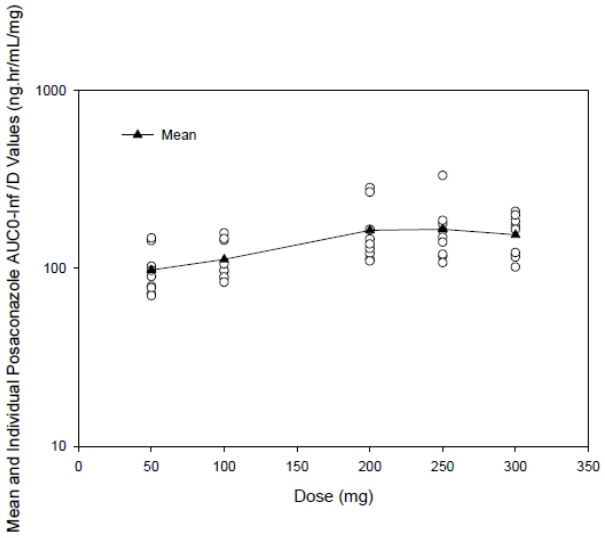
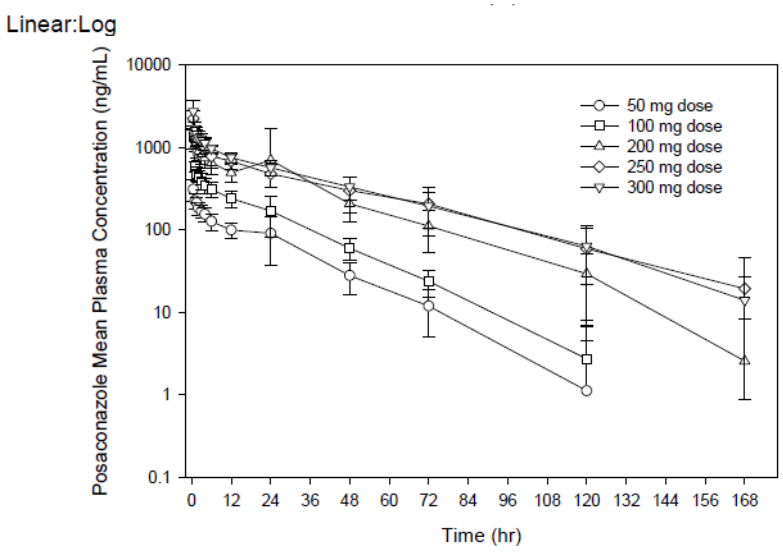


Figure 2. Arithmetic Mean MK-5592 (Posaconazole) Plasma Concentration-Time Profiles Following Single-Dose Administration of 50 – 300 mg Posaconazole Infusion



- The mean systemic clearance (CL) of POS was lower at doses equal to and above 200 mg (range: 6.54 - 6.90 L/hr) as compared to the lower doses (range: 9.40 - 10.9 L/h).
- Variability following POS IV solution infusion was moderate with CV% range of 26-30% and 26-50% for Cmax and AUCinf, respectively.
- A more than dose proportional increase in Cmax, AUC0-last, and AUC0-∞ occurs following POS IV solution infusion. This more than dose proportional increase mainly occurs at doses between 50 and 200 mg and less at the more clinically relevant doses from 200 - 300 mg.

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 investigational tablet compared to POS 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 POS tablet D following 8 days of daily administration of 300 mg and is not discussed.

Mean AUC0-last and AUC0-∞ for the POS tablet (tablet D) (22722 and 23647 hr*ng/mL, respectively) were approximately 2-fold smaller compared to the POS IV solution (42905 and 44380 hr*ng/mL, respectively). The mean maximum plasma concentration (Cmax) following the POS tablet administration was approximately 7- fold lower than Cmax after POS 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 POS tablet administration (CV 38% to 48%, respectively) than following POS 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 POS tablet than for the POS IV solution.

Table 6. Summary of POS 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.

Table 7. Statistical Assessment of Formulation Effect on the PK Profile of POS (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.

- POS mean AUC0-last and AUC0-∞ were approximately 2-fold smaller after POS tablet administration compared to the IV reference. POS mean Cmax was approximately 7-fold smaller. Mean elimination half-life was similar between both formulations.
- After a single dose of 300 mg POS IV solution, infused over 30 minutes, a mean Cmax of 4269 ng/mL (CV%=19%) was attained at a median Tmax of 0.5 hour. The mean exposure (AUCinf) was 44380 ng.h.mL (CV%=32%).
- The mean systemic clearance (CL) POS following POS IV solution infusion was 7.61 L/hr (CV%=41%) with a mean half-life of 29 hours.

- **Pharmacokinetics in target population**

Study P05520

Study design

Study P05520 was an open-label, sequential and parallel-group, multi-site study POS IV Solution used as prophylaxis in subjects at high risk for invasive fungal infections (IFIs). The study consisted of 4 sequentially-performed cohorts in Phase 1b (Cohorts 0, 1, and 2) and Phase 3 (Cohort 3). Overall, the study enrolled 279 high risk subjects, including 268 receiving at least 1 dose of POS IV solution. In all subjects, POS IV solution was administered via a central line as a 90-minute infusion.

Cohort 0

Subjects were randomized to receive either a single dose of POS IV solution or a single IV dose of placebo (5% dextrose in water [D5W]) administered via a central line as a 90-minute infusion. This was followed after approximately 12 h by POS oral suspension at a dose of 400 mg twice daily (BID) and subsequently for 11 additional doses of POS oral suspension given BID (6 days in total).

Cohorts 1 and 2:

In Cohort 1, subjects received IV POS solution at 200 mg BID on Day 1, followed by 200 mg once daily (QD) for another 13 days. In Cohort 2, subjects received IV POS solution at 300 mg BID on Day 1, followed by 300 mg QD for another 13 days. Thereafter, in both groups, subjects received POS oral suspension from Day 15 to Day 28 at a dose of 400 g BID.

PK Target for Final Dose Selection

The primary PK parameter of interest in this study was the plasma POS exposure at steady state (Cavg, or AUC[0-24] divided by 24 hours). A dose was to be selected for Cohort 3 based on the following criteria in the serial PK-evaluable cohorts from Cohorts 1 and 2:

• Mean steady-state Cavg of around 1,200 ng/mL (or AUC[0-24] of 28,800 ng.hr/mL) with at least 90% of the subjects within 2,500 ng/mL (or AUC[0-24] of 60,000 ng.hr/mL) and 500 ng/mL (or AUC[0-24] of 12,000 ng.hr/mL).

• No subject with mean Cavg at steady-state above 3,650 ng/mL (or AUC[0-24]above 87,600 ng.hr/mL).

• No subject with mean Cavg at steady-state below 200 ng/mL (or AUC[0-24] below 4,800 ng.hr/mL).

The desired exposure targets at steady state needed to be met in Cohorts 1 or 2 to allow for dose selection for Cohort 3.

Cohort 3:

Subsequently, in Cohort 3, POS IV solution was given for at least 5 days (300 mg BID on Day 1, followed by 300 mg qD) followed by POS oral suspension to complete 28 days of treatment. After IV therapy was completed, subjects were randomized to receive either 200 mg POS orally TID or 400 mg POS orally BID.

On Day 6, if the subject was able to tolerate oral medication, the subject had the option to begin treatment with a POS oral suspension dosing regimen as per randomized treatment assignment which was to be continued for up to 23 more days (28 days total treatment). The investigator may have switched the subject back to POS IV solution if the subject was unable to tolerate oral suspension. If the investigator felt that the subject would NOT be able to tolerate oral dosing on Day 6, the subject would continue on POS IV solution therapy until he/she was able to tolerate oral medications.

Cohort 3 Subjects with Expanded PK Sampling

Approximately 40 Cohort 3 subjects at selected sites received a minimum of 10 days of therapy with POS IV solution. On Day 11, the subject was switched to oral medication if possible and treatment continued as described above for cohort 3 patients.

There were two PK populations:

- the Serial PK-Evaluable Population, for which full PK profiles were evaluated and
- the Cmin PK-Evaluable Population, for which only Cmin was evaluated.

Pharmacokinetic Results

- Cohort 0 (200 mg single dose)

Table 8. Cohort 0: Single 200 mg POS IV Solution Infusion on Day 1, followed by 400 mg BID of POS Oral Suspenion for next 7 Days, Serial PK-evaluable Population

Cohort	Dose (mg)	Day	n	Cma (ng/mL)	Tma [a] (hr)	Interval (hr)	AUC(0-12) (hr ng/mL)	Cavg[b] (ng/mL)	Cmin (ng/mL)
0	200 mg (IV Solution)	1	10	881 (38)	1.42 (0.95-1.78)	12	5940 (37)	NA	318 (36)
	400 mg BID (oral suspension)	7	15	494 (36)	3.03 (2.73-5.13)	12	5080 (34)	423 (34)	370 (34)

a: Median (range)
b: Cavg AUC(interval)at steady state/dosing interval
NA- Not applicable
Source Data: [16.2.5.1.1] and [16.2.5.1.2]

- Cohort 1 (200 mg multiple dose)

Serial PK-Evaluable Population

Cavg calculated from serial PK sampling on Day 14 was available for 15 of the 16 serial PK evaluable subjects. The mean (%CV) Cavg achieved was 1180 ng/mL (51%), with individual values ranging from 525 to 3020 ng/mL. Arithmetic mean Cmin at steady state was 958 ng/mL (62%), with individual values ranging from 340-2795 ng/mL. Variability of exposure at steady state (AUC/Cavg) was around 50%.

Figure 3.

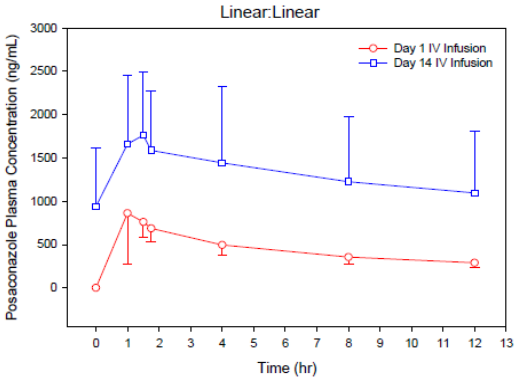


Table 9. Cohort 1: 200 mg BID IV Infusion of POS Solution on Day 1, then 200 mg QD of POS IV Solution for Next 13 Days, Serial PK-evaluable Population

Cohort	Dose (mg)	Day	n	Cma (ng/mL)	Tma [a] (hr)	Interval (hr)	AUC(Interval) (hr ng/mL)	Cavg[b] (ng/mL)	Cmin (ng/mL)
I	200 mg BID (IV Solution)	1	20	990 (47)	1.48 (1.0-3.97)	12	5390 (29)	NA	295 (38)
	200 mg QD (IV Solution)	14	15	1950 (50)	1.00 (1.0-4.02)	24	28200 (51)	1180 (51)	958 (63)

a: Median (range)
b: Cavg AUC(interval)at steady state/dosing interval
NA- Not applicable
Source Data: [16.2.5.1.4] and [16.2.5.1.5]

Table 10. Cohort 1: PK Parameters on Day 28, after 14 days of IV solution (200 mg QD, after BID on Day 1) Dosing from Days 1-14 and 14 days of POS 400 mg BID oral suspension from Days 15-28, Serial PK-evaluable Population

Cohort	Dose (mg)	Day	n	Cma (ng/mL)	Tma [a] (hr)	Interval (hr)	AUC(Interval) (hr ng/mL)	Cavg[b] (ng/mL)	Cmin
I	400 mg BID (oral suspension)	28	7	811 (26)	3.05 (0-8.13)	12	6920 (28)	570 (28)	532 (50)

a: Median (range)
b: Cavg AUC(interval)at steady state/dosing interval
Source Data: [16.2.5.1.7]

Disease State of Subjects	AML/MDS[a]	
	Cavg[b] (ng/mL)	Cmin[c] (ng/mL)
N	15	15
n (%) of subjects Cavg/Cmin ≥200 ng/mL and <500 ng/mL	0	3 (20%)
n (%) of subjects Cavg/Cmin ≥500 ng/mL and ≤2500 ng/mL	14 (94%)	11 (73%)
n (%) of subjects Cavg/Cmin >2500 ng/mL and ≤3650 ng/mL	1 (6%)	1 (7%)
n (%) of subjects Cavg/Cmin >3650 ng/mL	0	0

[a]AML/MDS=acute myelogenous leukemia/ myelodysplastic syndromes; [b]Cavg=AUCinterval/interval; n=number of subjects. [c]Cmin= Observed Cmin on Day 14; POS trough level immediately before a subject received the dose of POS on the day specified in the protocol; n=number of subjects.

Cmin PK-Evaluable Population

The mean Cmin values attained at Days 3, 6, 12 and 13 on IV solution and at Days 16, 19 and 25 on POS oral suspension are shown below. Variability is high, especially after POS oral suspension dosing. The Cmin values of subjects on maintenance dosing of POS oral suspension at 400 mg BID decreased approximately 30% as compared to the steady state exposure at 200 mg POS IV solution.

Table 11.

Cohort	Dose (mg)	Day	N	Cmin (CV)	Cmin 500 ng/mL
1	200 mg QD (IV solution)	3	16	627 (42)	44
		6	15	677 (58)	40
		12	16	896 (57)	25
		13	16	924 (60)	19
1	400 mg BID (oral suspension)	16	8	941 (80)	12.5
		19	9	639 (84)	56
		25	7	695 (43)	29

Source Data: [16.2.5.1.6], [16.2.5.1.8]

- Cohort 2 and 3 (300 mg multiple dose)

The PK data have been combined across the 2 cohorts (Cohort 2 and 3) for subjects included in the serial PK-evaluable cohorts. A total of 237 subjects were enrolled in Cohort 2 and 3. Of these 237 subjects, 49 were included in the serial PK-evaluable cohort.

Serial PK-Evaluable Population

Table 12. Cohort 2 and 3: POS Mean (%CV) PK Parameters on Days 10/14, after 300 mg BID Infusion of POS IV Solution on Day 1, then 300 mg QD, Serial PK-evaluable Population (Total and Per Underlying Condition)

Cohort	Dose	Day	n	Cmax (ng/mL)	Tmax[a] (hr)	AUCinterval (ng*hr/mL)	Cavg[b] (ng/mL)	Cmin (ng/mL)
2 and 3	All high risk subjects	10/14	49	3280 (74)	1.5 (0.98-4.0)	36100 (35)	1500 (35)	1090 (44)
	Per underlying condition							
	AML/MDS	10/14	30	3230 (77)	1.49 (0.98-4.00)	35400 (38)	1470 (38)	1050 (46)
	HSCT	10	19	3390 (71)	1.52 (1.00-2.00)	37500 (31)	1560 (31)	1170 (39)

a: Median (range) b: Cavg=AUC(interval)at steady state/dosing interval;
AML/MDS=acute myelogenous leukemia/ myelodysplastic syndromes; HSCT=hematopoietic stem cell transplant; n=number of subjects.

Based upon steady-state data from the 49 serial PK-evaluable subjects five subjects (10%) attained steady state Cmin values below 500 ng/mL. Forty-four (90%) subjects attained steady state Cmin values between 500 and 2500 ng/mL. No subject's Cmin value was above 2500 ng/mL.

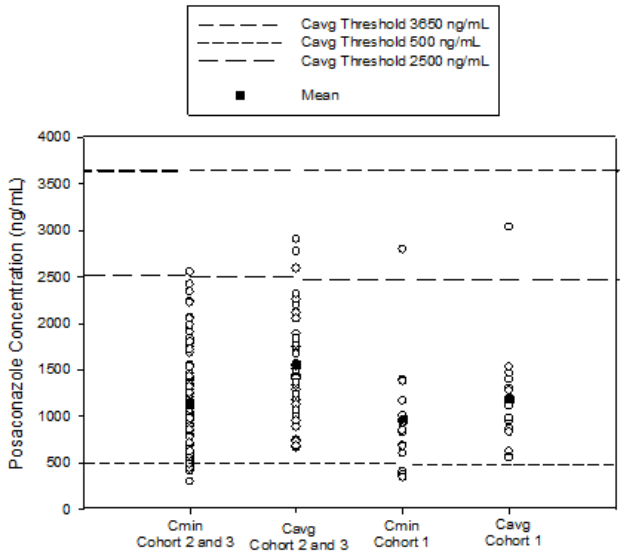
Table 13. Cohort 2 and 3: Frequency Distribution of Steady-State Cavg in Serial PK-Evaluable Subjects Following Multiple Dosing of POS IV Solution (300 mg), Overall and by Underlying Disease)

	Cavg (ng/mL)		
Disease State of Subjects	AML/MDS + HSCT	AML/MDS	HSCT
N	49	30	19
n (%) of subjects Cavg ≥200 ng/mL and <500 ng/mL	0	0	0
n (%) of subjects Cavg ≥500 ng/mL and ≤2500 ng/mL	46 (94%)	28 (93%)	18 (95%)
n (%) of subjects Cavg >2500 ng/mL and ≤3650 ng/mL	3 (6%)	2 (7%)	1 (5%)
n (%) of subjects Cavg >3650 ng/mL	0	0	0

AML/MDS=acute myelogenous leukemia/ myelodysplastic syndromes; Cavg= AUCinterval/interval;
HSCT=hematopoietic stem cell transplant; n=number of subjects.

All PK Cohorts (Cohorts 1, 2, and 3): Individual and Mean Steady-state Cavg and Cmin for the 200-mg (Cohort 1) and 300- mg Dose (Cohorts 2 and 3 combined) Groups of POS IV Solution - Serial PK- evaluable Population (P05520)

Figure 4.



Cmin PK evaluable Population

In Cohort 2, subjects received 300 mg POS IV solution for 14 days, followed by a maintenance dose of POS oral suspension at 400 mg BID for an additional 14 days (through Day 28).

The mean Cmin values attained at Days 3, 6, 12 and 13 on IV solution and at Days 16, 19 and 25 on POS oral suspension showed high variability for the later days and especially after POS oral suspension dosing. Despite this increased variability it is evident that trough plasma levels decrease significantly upon maintenance dosing with POS oral suspension (400mg BD).

In Cohort 3, all subjects were treated for a minimum of 5 days of POS IV solution. Thereafter, subjects were randomized to receive POS oral suspension either as 200 mg TID or 400 mg BID. Cmin values were collected from subjects on several days while on POS IV solution as well as during step down therapy to POS oral suspension. Variability in Cmin values was high (up to 50% for POS IV solution and higher for POS oral suspension).

In addition, the stepdown effect to oral therapy in Cohort 3 was randomized in a 1:1 ratio to receive POS oral suspension at either 200 mg TID (three times a day dosing; current recommended dose for prophylaxis) or 400 mg BID (twice a day dosing; current alternate dosing for treatment of IFIs). POS plasma levels decrease (up to 50%) after transitioning from POS IV solution to POS oral suspension, regardless of the dose regimen of POS oral suspension. However, the POS exposure was slightly higher when the sequential dose regimen of POS oral suspension was 200 mg TID.

Table 14. Cohort 3: Arithmetic Mean (%CV) of Cmin Values Following POS IV Solution 300 mg Dosing for at Least 5 Days, followed by POS Oral Suspension 200 mg TID or 400 mg BID dosing for up to 23 Days through Day 28 – Cmin PK-Evaluable Population, per Days on POS Oral Suspension (P05520)

Cohort	Dose (mg)	Days[a]	N	Cmin (%CV)	% Cmin <500 ng/mL[c]
3	300 mg QD (POS IV solution)	3	169	1073(42)	7
		6	108	1320 (44)	6
		8	56	1297 (44)	5
		Days [b]			
3	300 mg QD (POS IV solution), followed by 200 mg TID (POS oral suspension)	1-3	117	1253 (57)	15
		4-6	12	974 (58)	33
		7-10	37	1072 (74)	19
		>10	68	1126 (80)	28
3	300 mg QD (POS IV solution), followed by 400 mg BID(POS oral suspension)	1-3	103	1245 (55)	9
		4-6	10	657 (64)	30
		7-10	45	765 (55)	31
		>10	72	765 (59)	42

a: on POS IV solution; b: after transition to POS oral suspension ; n: number of subjects; c: % of subjects with mean Cmin values below 500 ng/mL

Comparison and Analyses of Results Across Studies

The clinical pharmacokinetics of POS IV solution is described based on two pooled analyses:

1) composite pharmacokinetic analysis

2) population PK model.

Composite pharmacokinetic analysis

Multiple dose PK in patients

The total variability of steady state pharmacokinetics in patient population was moderate to high with CV% of 39.7% for AUC0-24hr and 44.9% for Cmax, which was slightly higher than the variability in healthy subjects. The effect of age was consistent with effects seen in healthy volunteers. Compared to 200 mg, the dose normalized Cmax and AUC0-24hr were 11.6% and 18.8% lower for 300 mg, which is not statistically significant. There is a slightly lower Cavg and AUC0-24hr in AML patients compared to BMT patients that is not statistically significant. However, Cmax is statistically significant lower (25.8%) for AML compared to BMT.

Cmax is 45.9% higher for Females compared to Males, and Cavg is 22.5% higher for Females compared to Males. There was a statistically non-significant negative relationship between weight and Cmax, Cavg, and $AUC_{0\text{-}24hr}$. For every 10 kg increase in weight, $AUC_{0\text{-}24hr}$ would be expected to decrease by 1.8% and Cmax would be expected to decrease by 5.8%.

The weight effect on PK becomes clearer in the sensitivity analysis (Effect of Weight without Gender in the Model) compared to the original model, with a statistically significant relationship between weight and Cmax. For every 10 kg increase in weight, $AUC_{0\text{-}24hr}$ would be expected to decrease by 4.2% and Cmax would be expected to decrease by 10.0%. This indicates that gender may at least partly account for an effect of weight on exposure in patients.

Population PK model

The population PK model was developed on the basis of data from studies in healthy volunteers and high risk subjects in which intensive and sparse sampling was applied (overall dose range 50-300 mg in healthy volunteers, 200-300 mg in high risk subjects).

Primary objectives:

To develop a population PK model of POS IV solution using data in healthy volunteers and high risk subjects and quantify the variability of the PK of POS.

To perform a covariate analysis to identify the demographic and clinical factors that might affect POS exposure.

To translate the PK results from the study in high risk subjects (49 PK evaluable subjects in P05520) to a broader population by conducting simulations for a dose regimen of 300 mg QD after BID dosing on Day 1 and an infusion duration of 90 minutes

In total, 306 subjects (67 healthy volunteers and 239 high risk subjects) and 2322 plasma samples were available for the analysis. Covariates tested for their potential impact on pharmacokinetic parameters or model components were disease state (healthy volunteer (67), patient AML/MDS (166), and patient HSCT (73)), weight, gender, dose, and age.

Methods

The analysis was performed using non-linear mixed effects modeling methodology as implemented in NONMEM. First, a base model was developed, including a model for the random effects. Then a covariate analysis was added with forward addition and backward elimination of the non-significant covariates. The final model was checked for residual error model structure and outlier evaluation and then the model was validated using visual predictive check and bootstrap. In addition the derived parameters (Cmax, AUC, Cavg, Cmin) were calculated from the model predicted data and compared with those of the observed data.

Results

The data were best described by a 2-compartmental model with first order elimination. Covariate analysis showed 3 statistically significant covariates, weight on peripheral volume of distribution and disease status (healthy volunteers vs. patients) on both central and peripheral volume of distribution.

Variability was estimated for volumes, clearance and intercompartmental flow (52%, 22%, 44% and 50% for Vc, Vp, CL, and Q respectively).

Table 15. Final parameter estimates

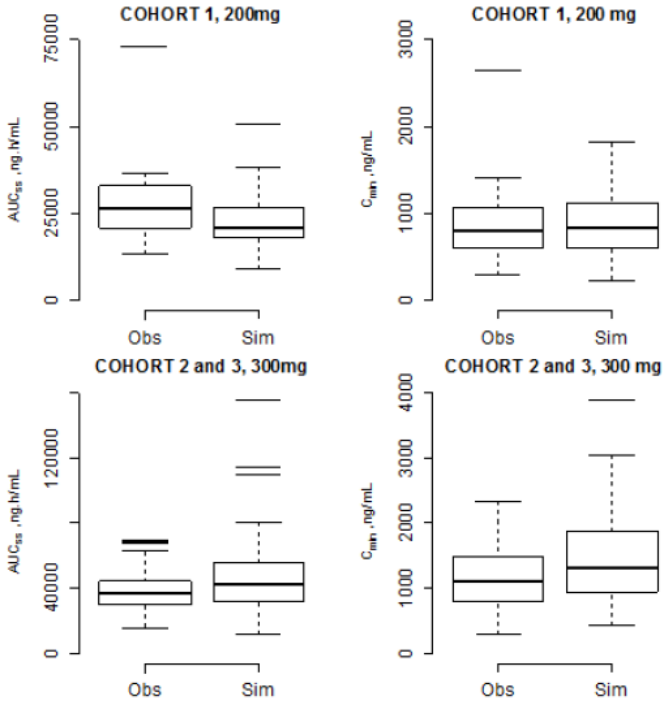
	OFV = -3731.58	
Parameter	**Estimate**	**RSE (%)**
Fixed effects		
CL (L/h)	7.78	3.01
Vc (L)	61.6	6.80
Q	93.5	9.26
Vp (L)	181	4.46
Weight on Vp	1.57	10.3
Patient on Vc	2.94	9.73
Patient on Vp	1.79	6.76
Non-Fixed effects		
IIV CL	43.9	11.2
IIV Vc	51.9	72.5
IIV Q	35.2	49.8
IIV Vp	22.0	29.5
IOV Vc	47.2	75.8
Residual		
Residual HV (STDEV)	0.385	5.86
Residual PAT (STDEV)	0.467	6.10

CL: clearance; V: volume of distribution; Q: intercompartmental flow; IIV: interindividual variability; IOV: interoccasion variability; STDEV: standard deviation; Vc: central compartment; Vp: peripheral compartment; OFV: Objective Function Value; RSE: relative standard error, calculated as Standard error/Final parameter estimate)*100

Simulated PK parameters

The final PK model is able to simulate PK parameters in high risk subjects comparable to the observed ones following administration of POS IV solution. Model qualification showed that the model was adequate and robust and could be used for simulation purposes and calculation of the relevant exposure parameters (AUC_T, Cavg, Cmin). Model derived Cavg and Cmin were compared against observed values in order to evaluate the performance of the model for the target population.

Figure 5. Boxplot Comparing Observed and Simulated PK Parameters AUCss and Cmin in High Risk Subjects administered with Multiple Doses of 200 or 300 mg Posaconazole IV Solution



Black line in box is median, whiskers are maximum and minimum without outliers. Horizontal lines represent outliers.

Accumulation with different doses and formualtions of posaconazole

Table 16. 1 Degree of Accumulation with Different Doses of Posaconazole Oral Intravenous Formulations in Healthy Volunteers (Oral suspension, Tablets, and IV Suspension) or Patients (IV Solution)

Formulation	Posaconazole Doses	Mean accumulation R (CV%)
Oral suspension*	50 mg BID	6.6 (29)
	100 mg BID	6.9(27)
	200 mg BID	7.6 (37)
	400 mg BID	8.3 (32)
Oral tablet**	200 mg QD	3.1 (24)
	200 mg BID	4.8 (28)
	400 mg QD	3.2 (57)
IV suspension***	100 mg QD	4.0 (16)
	200 mg QD	4.1 (21)
	400 mg QD	4.1 (15)
IV solution****	200 mg QD	3.6 (44)
	300 mg QD	2.8 (31)

*: I96-089; **: P05637 ; ***P02874; **** P05520 based on AUC0-24; R= accumulation factor, based on ratio of AUC at steady state to AUC on day 1 (AUC0-12 for BID; AUC0-24 for QD)
Source Data: I96-089, P05637; P02874; P05520

Comparison of Multiple Dose Pharmacokinetics for POS IV Solution with POS Oral Suspension in High Risk Subjects and rationale for chosen dose

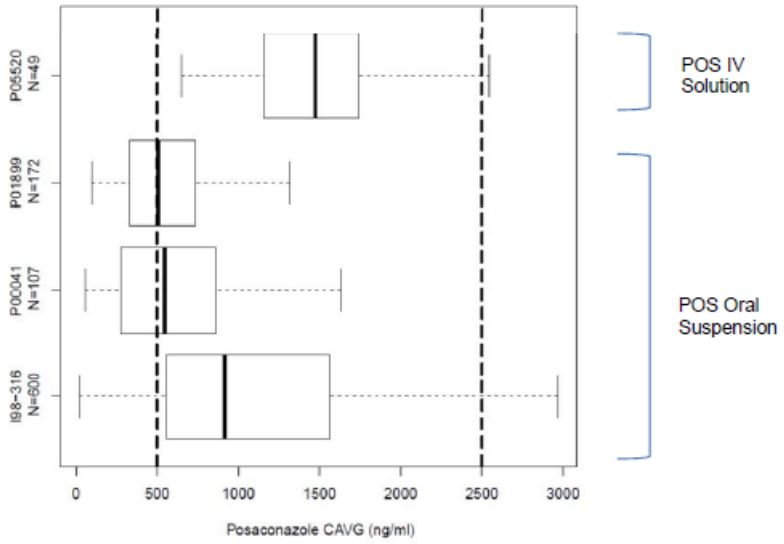
Observed plasma concentrations

Table 17. Cavg Quartile Analyses of Pivotal Patient Studies with POS IV Solution and POS Oral Suspension

	POS IV solution		POS oral suspension		
	P05520 prophylaxis in AML and HSCT		CI98-316 Prophylaxis in GVHD	P01899 Prophylaxis in Neutropenia	P00041 Treatment - Aspergillosis
	300 mg QD (Day 1 300 mg BID)		200 mg TID	200 mg TID	200 mg QID (hospitalized) then 400 mg BID
Quartile	Cavg range	Cmin range*	Cavg Range	Cavg Range	Cavg Range
Q1	649-1160	295-735	21.5 – 557	89.6 – 322	55 – 277
Q2	1218-1474	742-1120	557 – 915	322 – 490	290 – 544
Q3	1485-1745	1123-1410	915 – 1563	490 – 734	550 – 861
Q4	1803-2855	1415-2200	1563 - 3650	734 - 2200	877 – 2010

*: Cmin: the Cmin concentrations of Ctrough samples sampled before the next dose at steady state on day 10 or 14, analysis was added as a worst case scenario [Ref. 5.3.3.2: P05520]

Figure 6. Boxplot Comparing median and range of Cavg concentrations in High Risk Subjects administered with Multiple Doses of POS IV Solution] and POS Oral Suspension



Simulated plasma concentrations

Simulations were performed on the basis of the established population pharmacokinetic model, using a virtual population obtained through resampling of subject demographics from five patient studies from the POS program (oral suspension, investigational oral tablet and IV solution) ((P05615, P01899, C/I98-316, P00041, P05520).

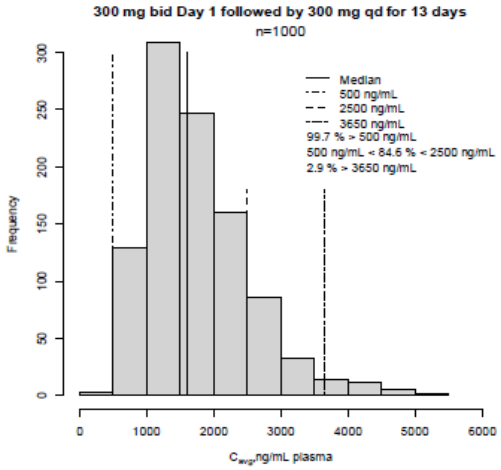
The simulation dataset included 1000 subjects and the significant covariate (weight) identified during model development was included in the dataset by external database resampling. The simulations included inter-individual variability and intra-individual variability (IOV) estimated in the final PK model. On Day 5, 10 or 13 (last day of dosing), a full PK profile was simulated for 1000 high risk subjects in order to calculate the individual exposure parameters AUC, Cavg, Cmin.

Simulations with high and low weight subjects did not show any difference in simulations and distributions on Cavg and Cmin. Simulation of high risk subjects (both AML/MDS as well as HSCT) for up to 13 days of dosing showed that:

- 99.7% and 93.6% of the high risk subjects have a Cavg and Cmin above 500 ng/mL, respectively
- 84.6% of the high risk subjects have a Cavg between 500 ng/mL and 2500 ng/mL;
- 15% of Cavg were above 2500 ng/mL, with 2.9% above 3,650 ng/mL

The simulations for the 5 days of dosing showed that 99.7% and 93.3% of the high risk subjects have a Cavg and Cmin above 500 ng/mL, respectively. In addition, 94.9% of the high risk subjects have a Cavg between 500 ng/mL and 2500 ng/mL; the remaining Cavg were generally above 2500 ng/mL but most remained below 3,650 ng/mL (0.1% was above 3,650 ng/mL.

Figure 7. Distribution of Simulated Cavg using the Weight Distribution based on all High Risk Subjects Treated with Posaconazole IV Solution after 13 days



The MAH concludes that the simulations indicate that a low percentage of the subjects may have Cavg exposures above 3650 ng/mL, but because there is no relationship between occurrence of (S)AE's or any other safety findings and POS exposure, this is considered not clinically relevant.

Thus, the simulations from the population PK model support the proposed marketed dose for POS IV solution for all subjects at high risk for obtaining IFIs.

Comparison of simulated exposures after 200mg and 300mg

Table 18. 3 Simulated Percentage of Subjects with POS Exposures (Cavg and Cmin) below 500 ng/mL, between 500 and 2500 ng/mL, between 2500 and 3650 ng/mL, and above 3650 ng/mL for Daily Dose of 200 and 300 mg (following BID dosing on Day 1) of POS IV Solution

	Cavg			
Treatment POS IV solution	**<500 ng/mL**	**500 – 2500 ng/mL**	**2500 – 3650 ng/mL**	**>3650 ng/mL**
200 mg	3.7	93.5	2.8	0
300 mg	0.3	84.3	12.4	3.0
	Cmin			
200 mg	34.8	65.1	0.1	
300 mg	12	86.5	1.4	0.1
Source data:simulation performed with the population PK model developed for POS IV solution (reference to M&S report 616)				

Weight adjusted dosing

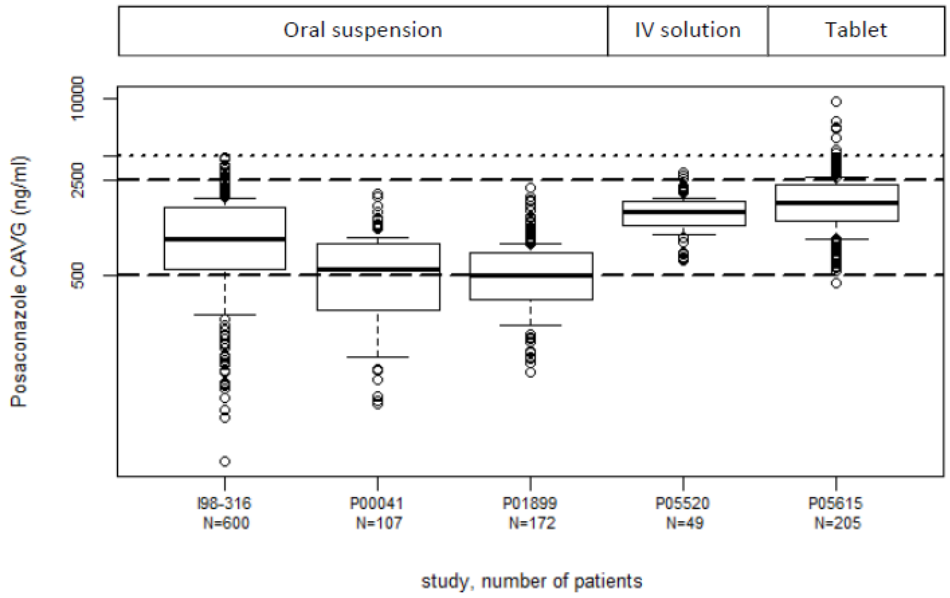
Weight-based dosing of 4 mg/kg does not reduce the percentage of subjects with Cavg above 3650 ng/mL, nor does it reduce variability (% CV). The exposures with the 4 mg/kg QD regimen are generally similar to those seen with the 300 mg QD dose.

Table 19. 1 Simulated Percentage of Subjects with POS Exposures (Cavg) below 500 ng/mL between 500 and 2500 ng/mL, between 2500 and 3650 ng/mL, and Above 3650 ng/mL and mean Cavg for the Daily Dose of 200 or 300 mg (following BID dosing on Day 1), and for a Weight-based Daily Dose of 4 mg/kg (following BID dosing on Day 1).

Treatment	**<500 ng/mL**	**500 – 2500 ng/Ml**	**2500 – 3650 ng/mL**	**>3650 ng/mL**	**Mean (ng/mL) (%CV)**
200 mg	3.7	93.5	2.8	0	1172 ng/mL (44%)
300 mg	0.3	84.3	12.4	3.0	1758 ng/mL (44%)
4 mg/kg	0.7	82.1	14.1	3.1	1776 ng/mL (48%)
Source data:simulations were performed with the existing population PK model for POS IV solution (reference to M&S report 616)					

Comparative exposure data of the three formulations

Figure 8.



2.4.3. Pharmacodynamics

Not applicable.

2.4.4. Discussion on clinical pharmacology

Bridging strategy

The bridging strategy had been accepted by CHMP in a scientific advice procedure and the exposure targets had been discussed. Similar (although not identical) PK targets have been used in the recently concluded application for posaconazole gastro-resistant tablets (X-028).

Exposure-response analysis from the pivotal trials for the oral suspension indicated an association between lower plasma concentrations and clinical failure. From the data provided from the prophylaxis trials, it appears that exposure in the lowest quartile was associated with poorer outcome, although low case numbers are a limiting factor. Equally, in the treatment of IFI, POS plasma concentrations presented from one trial tended to be higher in cases of clinical success, but the plasma concentration range was wide. Limited non-clinical data provide some additional support. The exposure target was to be within the ranges previously studied and demonstrated to be safe and effective. The strategy, which has been applied for the recently approved tablet formulation, is acceptable.

The bridging data as discussed at CHMP were based on Cavg, however this parameter is based on the AUC and will include what could be a significant proportion of the AUC in the initial distribution phase. The applicant recognised this and also included target attainment percentages based on Cmin data for the proposed regimen which is considered a more conservative parameter. The maximum plasma concentrations will be different following IV dosing and Cmax are discussed at the projected clinical dose in terms of safety (see section 2.6 below).

Cyclodextrin solubilizer

Posaconazole is a lipophilic drug and is difficult to formulate for intravenous administration. To improve aqueous solubitity, posaconazole IV solution contains the solubilizer Captisol (cyclodextrin, SBEβCD) which is also used in the IV formulation of another azole antifungal, voriconazole, at similar concentrations. The pH of the admixture solution is dependent on the posaconazole IV dose and typically ranges from 3.2 to 3.6. In the responses, the applicant provided data demonstrating that posaconazole is rapidly and quantitatively released from cyclodextrin after injection. The amount of cyclodextrin administered with IV POS is similar to the amounts administered with intravenous voriconazole, at least for patients weighing > 60kg, which represents the majority of patients. This appears acceptable as it is expected that IV POS will be administered over relatively short periods of time and provided the product information includes a comment of caution for use in patients weighing less than 60kg. Because of accumulation in patients with renal impairment, cyclodextrin containing products are not generally suitable in this population and this should be clearly stated in the SmPC.

Phase I study programme

POS IV solution is intended for administration via a central line as local infusion-site reactions were identified in non-clinical studies and confirmed in clinical study in healthy volunteers. Nevertheless, POS IV solution was administered via peripheral infusion in all healthy volunteer studies. Despite a change in administration time (reduced from 90 to 30 minutes), both multiple dose studies (P04985 and P06356) had to be terminated prematurely due to local safety and tolerability problems with the IV solution. Consequently the healthy volunteers data consist of single dose data only, which is a significant limitation as accumulation has been demonstrated for POS oral suspension.

POS is distributed to extravascular compartments and slowly eliminated after administration of single doses of the IV solution, similarly to the oral suspension. Tmax is reached around the time of termination of infusion. AUCinf was comparable for POS IV solution and POS oral suspension (when taken with a high fat meal) at the 100 mg dose level, but approximately 3 times higher as compared to the POS oral suspension in the fasted state. Cmax is approximately 5-7 times higher for the POS IV solution compared to the oral suspension. T1/2 after a single dose of 100 mg was comparable to POS oral suspension (fed) (20 and 25 hours, respectively). Single dose data indicate a more than proportional increase of Cmax and AUC in the lower dose range (< 200mg). AUC increases approximately dose proportionally between doses of 200mg and 300mg, while Cmax seems to increase less than proportionally. The difference in CL at higher doses may be due to saturation of elimination of POS, and in this case may be a factor in the apparent non-linearity of the PK. POS oral suspension reportedly shows linear kinetics following single- and multiple-dose administration up to 800 mg.

Posaconazole administered as an oral suspension was shown to accumulate more than expected after multiple doses, an effect thought to be at least in part due to the difference in food intake over time.

Multiple dose PK data are not available for IV POS in healthy volunteers.

Accumulation was also seen with the oral gastro-resistant tablet formulation of posaconazole recently evaluated in another line extension procedure (X-028).

The phase I programme is significantly affected by the lack of multiple dose data, in particular as time dependency is described for oral posaconazole formulation.

PK in target population

The patient population appears representative of the majority of patients who are at risk of developing IFIs. The population selected for this cohort was the same for which POS oral suspension is approved in

the prevention of IFIs. The study population is representative of the population expected to use POS for prophylaxis of IFIs. In their responses, the applicant provided data to suggest that exposure in the treatment population may be expected to be similar to that in the prophylaxis population, thus supporting the applicability of the data generated for the population with actual IFI. This addresses the Major Objection raised during the initial assessment.

Single dose PK are difficult to compare to healthy volunteers due to the different time intervals, but exposures appear to be lower in patients and certainly Cmax is lower, as seen with the oral suspension.

Regardless of formulation, posaconazole demonstrates greater than expected accumulation after multiple dosing, which is likely due to reduced clearance. Accumulation with the intravenous solutions appears less than with the oral formulations, possibly due to the elimination of the food effect. Data may be affected by the proportion of patients not dosed to steady state with the intravenous formulation.

Data suggested that there may be time-dependency in the PK of posaconazole, however further exploration did not confirm this based on the available data. The variability in exposure (AUC/Cavg) for IV POS was around 50%. The PK of oral posaconazole differ between patients and healthy volunteers and even between patient groups depending on the underlying condition. After multiple IV posaconazole doses in patients, there was no significant difference between patients with AML/MDS and HSCT in exposure, providing support for the assumption that bioavailability and effect of food is the main cause of the observed difference with the oral formulation.

Dose finding

The observed data (serial PK evaluable patients) for both the 200mg and 300mg dose show that the predefined exposure target was met for Cavg (94% of patients had Cavg between 500- 2500ng/ml for both dose levels) and exposure after IV POS solution was higher than seen after the oral suspension. The simulated data show that a higher proportion of subjects meet the exposure target with the 200mg dose, primarily due to the fact that a higher proportion of patients will have exposures between 2500 and 3650ng/ml with the 300mg dose. The applicant proposes the 300mg dose based on the significantly higher number of patients expected to have a Cmin < 500ng/ml with the 200mg dose (35% versus 12%), although Cmin was not the primary bridging parameter.

The simulated data at the 300mg dose level indicate that around 15% of patients will have exposures exceeding the upper exposure target of 2500 ng/ml after 13 days of treatment, with around 3% exceeding the upper threshold of 3650ng/ml. Reported exposures resulting from the 300mg intravenous solution were very similar to those resulting from the 300mg tablet, which was recently approved.

While Cmin was not the primary bridging parameter, it is agreed to be a more conservative target in terms of improved efficacy and, taking the lack of demonstrated increase in adverse events into account, the 300mg dose is considered acceptable. The on-going comparative study with posaconazole intravenous solution and the tablet formulation (PN 069) will generate additional PK, efficacy and safety data and if necessary the question of the most appropriate dose will be revisited in the light of the emerging data.

Composite PK analysis and population PK indicate that gender and weight may affect exposure to IV POS, but weight adjusted dosing did not relevantly affect the proportion of subjects meeting the exposure target.

2.4.5. Conclusions on clinical pharmacology

In summary, single dose PK in healthy volunteers and single and multiple dose PK in patients for IV POS solution have been described. A population PK model was developed to further characterise PK

parameters and relevant co-variates. The characterization of the pharmacokinetics of IV POS solution is generally satisfactory. Composite PK analysis and population PK indicate that gender and weight may affect exposure to IV POS solution. IV POS solution in a dose of 200mg and 300mg will lead to higher plasma concentrations than POS oral suspension. The 300mg dose IV is expected to result in exposures similar to those of the 300mg tablet.

2.5. Clinical efficacy

There was no clinical study with efficacy as the primary endpoint in this application.

2.5.1. Main study

P05520 : Pharmacokinetics, Safety and Tolerability of Intravenous Posaconazole Solution followed by Oral Posaconazole Suspension in Subjects at High Risk for Invasive Fungal Infections.

Methods

Study P05520 was an open-label, sequential- and parallel-group, multi-site study POS IV Solution used as prophylaxis in subjects at high risk for invasive fungal infections (IFIs). The study consisted of 4 sequentially-performed cohorts in Phase 1b (Cohorts 0, 1, and 2) and Phase 3 (Cohort 3).

In all subjects, POS IV solution was administered via a central line as a 90-minute infusion.

Study Participants

Subjects with expected neutropenia due to chemotherapy for AML, MDS, or secondary leukemias (cohorts 0,1,2), and in addition recipients of allogeneic HSCT (cohort 3 only) were selected to participate in the trial. Subjects had to be anticipated (likely to develop within 3 days to 5 days) or documented prolonged neutropenia (absolute neutrophil count [ANC] <500/mm3 [0.5 x 109/L]) at Baseline and likely to last for at least 7 days. Subjects were required to have a central line catheter in place. Subjects could have received a single infusion via a peripheral line if a central line catheter was not available.

Treatments

Treatment duration/ exposure:

Cohort 0: POS 200 mg IV or placebo, single dose, followed by POS oral suspension 400mg BD for of 6 days

Cohort 1: POS 200 mg IV, (200 mg BID on Day 1, followed by 200 mg qD for another 13 days), followed by POS oral suspension 400mg BD for 14 days

Cohort 2: POS 200 mg IV, (200 mg BID on Day 1, followed by 200 mg qD for another 13 days), followed by 200 mg qD for another 13 days), n=21, followed by POS oral suspension 400mg BD for 14 days

Cohort 3: POS 300 mg IV, (300 mg BID on Day 1, followed by 300 mg qD for at least 4 days), followed by POS oral suspension 200mg TID or 400mg BD for a total of 28 days

Outcomes/endpoints

There were no primary efficacy endpoints in any of the cohorts. For Cohort 3, the following endpoints were to be summarized using descriptive statistics for all subjects combined and by underlying disease:

1) Clinical failure during the exposure phase as determined by incidence of IFIs as diagnosed by the investigator, deaths up to Day 70, discontinuations for any reasons, or use of systemic antifungals for empiric treatment of fungal infections for more than 4 days; (Of note, the protocol allowed subjects to receive an IV amphotericin B formulation or an echinocandin as empirical treatment for up to 4 days for possible fungal infections and remain on study therapy

2) Survival Assessment at Day 60 (at any day from Days 60 to 70).

Safety assessments

For cohort 1 and 2, Safety assessments were collected at Baseline, Day 1 (pre-dose), Day 3, Day 7, Day 14 or EOT (end of the IV Treatment Phase), Week 3,Week 4 or EOT (end of the Oral Treatment Phase), and Follow-up (7 days after last dose of study drug). Similar timelines were followed for cohort 0.

Safety assessments for cohort 3 (hematologic studies and serum chemistries) were collected at Baseline, Day 1 (pre-dose), Day 3, Day 6, Day 8, Day 10 (±2 days), Day 15 (±3 days), Day 22 (±3 days), Day 28 or EOT, and Follow-up (7 days after last dose of study drug).

Sample size

Overall, the study enrolled 279 high risk subjects, including 268 receiving at least 1 dose of POS IV solution.

The overall sample size selected for this study was based on PK considerations.

Results

For the purpose of efficacy assessment, the two 300 mg dose cohorts (Cohort 2 and 3) have been combined.

Among the 21 subjects in the POS IV solution 200 mg multiple dose group (Cohort 1), there were 7 subjects (33%) who developed clinical failure. One (1/21) (5%) subject had a proven (fatal) IFI diagnosed during the period of the study.

Among the 237 subjects in the POS 300 mg multiple dose group (Cohort 2 and 3 combined), there were 75 subjects (32%) who developed clinical failure; in most cases this was due to discontinuation of study therapy for reasons other than treatment failure. Three (3) (<1%) subjects was reported as having a proven or probable IFI and 3 (1%) subjects received systemic antifungals for empiric treatment of fungal infections. Overall, the incidence of IFI in the pivotal study of POS IV solution, P05520, was low and similar to that previously reported for POS oral suspension in P01899 and C/I98-316.

It is particularly noteworthy to examine the incidence of proven/probable IFI and the requirement of empirical antifungal treatment, as these two components of the clinical failure endpoint can be viewed as focusing specifically on “true” treatment failures related to ineffective antifungal prophylaxis.

There were no (0%) IFIs reported in Cohort 0. In the 200 mg multiple dose group (Cohort 1), there was one subject (5%) with a reported proven or probable IFI. In the 300 mg dose group (Cohorts 2 and 3 combined), there were three subjects (1%) with a reported proven or probable IFI.

No subjects in either of the two 200 mg dose groups (Cohorts 0 & 1) and six subjects (2.5%) in the 300 mg dose group (Cohorts 2 and 3 combined) received systemic antifungals for the empirical treatment of fungal infections for more than 4 days while on study drug. Of the six subjects, four of the subjects had AML or MDS as their underlying disease and two subjects entered the study after HSCT.

Table 20. Components of Clinical Failure 300 mg Dose Group (Cohorts 0 and 1) in P05520

Clinical Failure 300mg Dose Subjects (Cohorts 2 and 3)			
	Cohort 2 POS IV 300mg multiple dose followed by oral POS 400mg BID n=24	Cohort 3 POS IV 300mg multiple dose followed by oral POS 200mg TID or oral POS 400mg BID n=213	**Total** (Cohorts 2 and 3) n 237
	n (%)	n (%)	n (%)
Overall Clinical Failure[a]	**(38)**	**(31)**	**5 (32)**
Proven or Probable IFI	1 (4)	2 (1)	3 (1)
Use of Empirical Antifungal Treatment	1 (4)	5 (2.3)	6 (2.5)
Confirmed Deaths	3 (12)	13 (6)	16 (7)
Discontinued Treatment Phase[b]	7 (29)	60 (28)	67 (28)

n number of subjects; POS posaconazole

[a] The overall clinical failure row counts a subject only once, even though a single subject may be counted in multiple subcategories for reasons of clinical failure. Specifically, all 3 subjects in the subcategory of Proven or probable IFI are also counted in the subcategory of Discontinued Treatment Phase . One of the subjects (Subject No. 9/000341) in the Proven or probable IFI subcategory also died from the IFI and is thus counted in three subcategories. Two of the subjects (Subject Nos. 35/000414 and 86/000427) who received empirical antifungal treatment are also counted in the subcategory of Discontinued Treatment Phase . Eleven of the deaths (Subject Nos. 2/000320, 5/000303, 6/000207, 6/000721, 8/000206, 9/000341, 9/000682, 11/000712, 29/000368, 35/000311, and 38/000361) are also counted in the subcategory of Discontinued Treatment Phase because the deaths occurred during the treatment phase.

[b] Among the 67 discontinuations across Cohorts 2 and 3, 5 were due to treatment failure. Among the 5 discontinued due to treatment failure, 4 (Subject Nos. 3/000653, 4/000651, 17/000359, and 23/000679) were due to possible IFIs and 1 (Subject No. 17/000339) was due to a probable/proven IFI. The reason for discontinuation of study therapy specified by the investigator for the other 2 subjects with probable/proven IFIs (Subject Nos. 7/000202 and 9/000341) was adverse event . Detailed subject narratives are provided in Section [14.6.2]

Survival

In Cohort 0, 90% of subjects treated with POS IV and 91% of subjects treated with Placebo IV survived through Day 65. In Cohort 1, 95% of subjects treated with multiple doses of 200 mg POS IV survived through Day 65 and 89% of subjects in the 300-mg dosing group (Cohorts 2 and 3 combined) were confirmed to be alive at Day 65.

Nine of the 13 confirmed deaths among subjects in Cohort 3 had AML or MDS as underlying disease; the remaining four deaths were in recipients of allogeneic HSCT. In addition to the 16 confirmed deaths, another 11 subjects (all in Cohort 3) were missing the Day 65 Survival Assessment. Therefore, 89% (210/237) subjects were confirmed to be alive at the Day 65 Survival Assessment. Three additional deaths were reported during the follow-up period (after completion of the treatment period, i.e. after Day 70).

2.5.2. Discussion on clinical efficacy

The open, non-comparative study P05520 was not designed as a clinical efficacy study, but aimed to investigate the PK of the intravenous solution of posaconazole in patients and to provide additional safety data. The study population included patients with AML/MDS and anticipated or proven neutropenia (<500/mm^3 for at least 7 days and HSCT recipients (cohort 3 only), with the aim to enrol patients representative of the target population for antifungal prophylaxis with posaconazole. Patients with

moderate or severe renal impairment (CLCrea < 50ml/min) were excluded from the study due to the restricted use of cyclodextrin in this population.

The study design, including lack of a control group and short study duration may be acceptable with regards to the primary endpoint (and had been accepted by CHMP during scientific advice), but limits efficacy and in particular safety data evaluation.

The clinical endpoint was a composite endpoint including proven or suspected IFI, discontinuation of treatment, > 4 days of non-study antifungals, and death. The criteria for diagnosis of an IFI were not clearly presented (investigator's decision) and there was no adjudication. The usefulness of this composite endpoint is limited.

The rate of clinical failures as defined was high, around one third of patients developed "clinical failure", primarily due to treatment discontinuation.

The rate of breakthrough invasive fungal infections was low. Comparisons between the 200mg and 300mg dose levels are not meaningful due to the low numbers at the 200mg dose level.

In the 300mg dose group, 3 (1%) patients had a proven IFI, while 6 (2.5%) received > 4 days of non-study antifungal treatment.

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 duration of treatment and follow-up in study P05520 were shorter than in C/198/316.

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.

2.5.3. Conclusions on the clinical efficacy

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, it is difficult to draw firm conclusions from these results.

2.6. Clinical safety

Posaconazole concentrate for solution for infusion is an aqueous injectable solution containing 18 mg/mL of POS to be diluted with sodium chloride 0.9% or 5% dextrose in water prior to IV administration. The primary excipient in POS IV solution is sulfobutylether-β-cyclodextrin (SBEβCD, marketed as Captisol), an excipient that is found in marketed IV products including authorised voriconazole IV formulation. This excipient solubilizes posaconazole by formation of soluble complexes. When solubilized as POS IV solution, the pH of the formulation is approximately 2.6 and when admixed with 0.9% sodium chloride or 5% dextrose in water, the admixture solution for administration ranges from a pH of 3.1 to 3.6. It should be noted that SBEβCD has been associated with kidney toxicity in rat models, however, the overall amount of SBEβCD in the POS IV solution is anticipated to be similar to or lower than that administered with IV voriconazole.

Safety in healthy volunteers

All doses in healthy volunteers were administered via a peripheral vein. When administered peripherally over 90 minutes, POS IV solution caused unacceptably high rates infusion-site reactions, which were observed in 6 out of 9 patients. The reaction occurs with a delay, and takes days to resolve. Suspected

extravasation was observed in 1 subject, the same subject also experienced liver function test abnormalities. Cmax in this subject was lower than for the remaining patients (and Tmax delayed), while AUC was in the range observed.

After decreasing the infusion time to 30 minutes, IV POS solution was better tolerated, but injection site reactions were still frequent and significant enough to prevent multiple dose studies in healthy. The pH of the suspension formulation was between 6.0 and 8.0. Local intolerability may well be associated with the low pH of the infusion solution, although it seems unlikely that the pH alone is causative, as other solutions with similar pH cause less local toxicity.

Arrhythmia and heart failure have been associated with azoles agents and are considered a class effect of azoles, but have not been observed with either oral or IV suspension POS formulations. However, the MAH conducted Echocardiograms in study P06356 as a faster infusion (30 minutes) and consequently higher plasma concentrations may cross an effect threshold.

Decreases in ejection fraction (EF) seen in Echocardiograms of healthy volunterrs were small and transient, although more significant changes is patients with impaired myocardial function cannot be ruled out. Decreases in EF seem to be associated with Cmax.

Safety in patients

Patient exposure

Overall, 268 subjects have received POS IV solution in the pivotal Phase 1b/3. This included 10 high-risk subjects who received a single 200 mg dose of POS IV solution, 21 high-risk subjects who received multiple dosing of 200 mg POS IV solution (following 200 mg BID on Day 1), and 237 high-risk subjects who received multiple dosing of 300 mg daily (following 300 mg BID on Day 1). The targeted subject population that was enrolled in P05520 was representative of the majority of patients.

Table 21. Duration of Treatment: Interval from Beginning to End of Treatment, IV Phase, Cohorts 2 and 3 [300 mg]

	Cohort 2/ Cohort 3 IV 300mg n=237	
Duration (day)		
Received any treatment	237	(100)
>= 1	237	(100)
>= 2	237	(100)
>= 3	234	(99)
>= 4	230	(97)
>= 5	227	(96)
>= 6	141	(59)
>= 8	130	(55)
>= 10	117	(49)
>= 15	67	(28)
>= 22	24	(10)
>= 28	12	(5)
Statistics (day)		
n	237	
Mean	11.2	
SD	7	
Median	9	
Min	2	
Max	28	

Note that duration is based on treatment begin date and IV end date and does not take into account possible dosing interruptions and subject noncompliance.

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

Adverse events

In the 200 mg multiple dose group (Cohort 1), almost all subjects experienced at least one treatment Emergent Adverse event (TEAE) (20/21 subjects [95%]), with 3 subjects (14%) reporting a treatment-related TEAE. Severe or life-threatening TEAEs were reported for 11 subjects (52%) and 4 subjects (19%) discontinued study drug due to a TEAE. Overall, in the 200 mg dose group, an SAE was reported for 4 subjects (19%), with one death (5%). Among subjects in the 200-mg multiple dose group (Cohort 1), the overall incidence of specific TEAEs, the incidence of those reported with an onset during the IV phase, and the incidence of those reported with an onset during the Oral phase were all similar to those commonly reported with POS oral suspension.

In the 300 mg multiple dose group (Cohorts 2 and 3), almost all subjects reported at least one TEAE (235/237 subjects [99%]) with 90 subjects (38%) reporting a treatment-related TEAE during either the IV or oral phase, with 72 subjects (30%) experiencing at least one treatment-related TEAE during the IV phase. The most commonly reported treatment-related TEAEs during the treatment phase (IV or Oral phases) were diarrhea (9%), nausea (8%), rash (6%), vomiting (5%), and hypokalemia (5%). The most commonly reported treatment-related TEAEs during the IV phase were diarrhea (8%), nausea (5%), rash (5%), vomiting (4%), and hypokalemia (4%). In comparison with the prior POS oral suspension prophylaxis study of neutropenic subjects, 34% of TEAEs were judged related to study drug, and the most

common treatment-related TEAEs included nausea and diarrhea, reported in 22/304 subjects (7%) and 20/304 subjects (7%), respectively.

Table 22. Summary of Adverse Experiences, All Treated Subjects, Cohort 1- 3 in P05520

	Cohort 1 POS IV 200mg n=21	
Category		
Treatment Emergent AE	20	(95)
Treatment-Related Treatment Emergent AE	3	(14)
Serious AE	4	(19)
Death	1	(5)
Severe/Life-Threatening Treatment Emergent AE	11	(52)
Study Drug Discontinuation due to AE	4	(19)

n = number of subjects; POS = Posaconazole
Note: Deaths are also included in Serious Adverse Experiences count.

	Cohort 2/ Cohort 3 IV 300mg n=237	
Category		
Treatment Emergent AE	235	(99)
Treatment-Related Treatment Emergent AE	90	(38)
Serious AE	71	(30)
Death	19	(8)
Severe/Life-Threatening Treatment Emergent AE	123	(52)
Study Drug Discontinuation due to AE	45	(19)

Table 23.

Table 49- 3 Summary of Treatment Related Treatment Emergent Adverse Events By Quartiles (≥2% Incidence), All Treated Subjects, By Descending Frequency, Serial PK-Evaluable Population Number (%) of Subjects (Protocol No. 05520)

	Quartile 1 n=16		Quartile 2 n=16		Quartile 3 n=16		Quartile 4 n=16	
Adverse Event								
Diarrhoea	0	(0)	3	(19)	1	(6)	1	(6)
Rash	0	(0)	2	(13)	1	(6)	1	(6)
Hypokalaemia	0	(0)	0	(0)	2	(13)	1	(6)
Vomiting	0	(0)	2	(13)	0	(0)	1	(6)
Alanine Aminotransferase Increased	0	(0)	2	(13)	0	(0)	0	(0)
Headache	0	(0)	2	(13)	0	(0)	0	(0)
Hypertension	0	(0)	2	(13)	0	(0)	0	(0)
Hypomagnesaemia	0	(0)	0	(0)	2	(13)	0	(0)
Nausea	0	(0)	1	(6)	0	(0)	1	(6)
Pruritus	0	(0)	0	(0)	1	(6)	1	(6)
Rash Maculo-Papular	0	(0)	2	(13)	0	(0)	0	(0)
Abdominal Discomfort	0	(0)	0	(0)	1	(6)	0	(0)
Abdominal Pain	0	(0)	0	(0)	0	(0)	1	(6)
Anorectal Discomfort	0	(0)	0	(0)	1	(6)	0	(0)
Aspartate Aminotransferase Increased	0	(0)	1	(6)	0	(0)	0	(0)
Atrial Flutter	1	(6)	0	(0)	0	(0)	0	(0)
Blood Alkaline Phosphatase Increased	0	(0)	1	(6)	0	(0)	0	(0)
Chest Discomfort	0	(0)	0	(0)	1	(6)	0	(0)
Confusional State	1	(6)	0	(0)	0	(0)	0	(0)
Dermatitis	0	(0)	0	(0)	1	(6)	0	(0)
Epigastric Discomfort	1	(6)	0	(0)	0	(0)	0	(0)
Erythema	0	(0)	0	(0)	1	(6)	0	(0)
Febrile Neutropenia	0	(0)	0	(0)	1	(6)	0	(0)
Fluid Overload	0	(0)	0	(0)	1	(6)	0	(0)
Gamma-Glutamyltransferase Increased	0	(0)	1	(6)	0	(0)	0	(0)
Hepatic Function Abnormal	1	(6)	0	(0)	0	(0)	0	(0)
Hepatotoxicity	1	(6)	0	(0)	0	(0)	0	(0)
Hypoglycaemia	0	(0)	1	(6)	0	(0)	0	(0)
Hypophosphataemia	0	(0)	0	(0)	1	(6)	0	(0)
Neck Pain	0	(0)	1	(6)	0	(0)	0	(0)
Oedema Peripheral	0	(0)	0	(0)	1	(6)	0	(0)
Petechiae	0	(0)	0	(0)	1	(6)	0	(0)
Photophobia	0	(0)	0	(0)	1	(6)	0	(0)
Pulmonary Mycosis	0	(0)	1	(6)	0	(0)	0	(0)
Pyrexia	0	(0)	1	(6)	0	(0)	0	(0)
Renal Failure Acute	0	(0)	0	(0)	1	(6)	0	(0)
Skin Lesion	0	(0)	1	(6)	0	(0)	0	(0)
Tachycardia	1	(6)	0	(0)	0	(0)	0	(0)
Thrombophlebitis	0	(0)	1	(6)	0	(0)	0	(0)
Source data: P05520								

Serious adverse events and deaths

SAEs were reported for 71 subjects (30%), with 27 of these subjects (11%) reporting an SAE with an onset during the IV phase. The only SAE terms with an onset during the IV phase reported by more than one subject were sepsis (3 subjects), renal failure acute (3 subjects), respiratory distress (2 subjects), respiratory failure (2 subjects), and subarachnoid hemorrhage (2 subjects).

There were a total of 19 deaths that occurred in the subjects in the 300 mg multiple dose groups (Cohorts 2 and 3), with 10 deaths occurring during the IV Phase and 7 deaths occurring during the Oral phase. There were an additional two deaths that occurred during the follow-up period. There were no causes of death in Cohorts 2 and 3 (300 mg multiple dose) that were determined to be related to study treatment by the investigator.

Table 24. Summary of Serious Treatment Related Adverse Experiences,Cohorts 2 and 3 [300 mg]

	Cohort 2/ Cohort 3 IV 300mg **TOTAL** n=237		Cohort 2/ Cohort 3 IV 300mg **IV Phase** n=237		Cohort 2/ Cohort 3 IV 300mg **Oral Phase** n=170	
SUBJECTS REPORTING ANY ADVERSE EXPERIENCE	3	(1)	2	(1)	1	(1)
GASTROINTESTINAL DISORDERS	1	(<1)	0		1	(1)
NAUSEA	1	(<1)	0		1	(1)
VOMITING	1	(<1)	0		1	(1)
HEPATOBILIARY DISORDERS	1	(<1)	1	(<1)	0	
HYPERBILIRUBINAEMIA	1	(<1)	1	(<1)	0	
INFECTIONS AND INFESTATIONS	1	(<1)	1	(<1)	0	
PULMONARY MYCOSIS	1	(<1)	1	(<1)	0	

Table 25.

Table 49- 5 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. P05520)

	POS 300 mg Cmin ≤ 2,500 ng/mL n=126		POS 300 mg Cmin > 2,500 ng/mL n=3	
Category				
Treatment Emergent AE	126	(100)	2	(67)
Treatment-Related Treatment Emergent AE	55	(44)	1	(33)
Serious AE	38	(30)	1	(33)
Death	10	(8)	0	(0)
Severe/Life-Threatening Treatment Emergent AE	73	(58)	2	(67)
Study Drug Discontinuation due to AE	24	(19)	0	(0)
Data source: Appendix 1-Table 5				

Discontinuation due to adverse events

45 subjects (19%) in the 300 mg dose group discontinued study drug due to a TEAE. Of these, 29 subjects (12%) discontinued study drug due to a TEAE with an onset occurring during the IV phase and 14 subjects (8%) discontinued study drug with an onset occurring during the Oral phase.

The only specific TEAEs leading to discontinuation of study drug with an onset occurring during the IV phase reported by more than one subject were acute myeloid leukemia (AML) (3 subjects), electrocardiogram QT prolonged (2 subjects), and rash (2 subjects).

13 subjects (5%) reported treatment-related TEAEs leading to discontinuation of study drug. Of these, 8 subjects (3%) discontinued study drug due to a TEAE with an onset during the IV phase.

Table 26. Summary of Treatment related AEs to Study Drug Discontinuation, (Cohort 2-3)

	Cohort 2/ Cohort 3 IV 300mg **TOTAL** n=237		Cohort 2/ Cohort 3 IV 300mg **IV Phase** n=237		Cohort 2/ Cohort 3 IV 300mg **Oral Phase** n=170	
SUBJECTS REPORTING ANY ADVERSE EXPERIENCE	13	(5)	8	(3)	4	(2)
CARDIAC DISORDERS	1	(<1)	0		1	(1)
ATRIAL FIBRILLATION	1	(<1)	0		1	(1)
GASTROINTESTINAL DISORDERS	2	(1)	2	(1)	0	
ABDOMINAL PAIN	1	(<1)	1	(<1)	0	
DIARRHOEA	1	(<1)	1	(<1)	0	
HEPATOBILIARY DISORDERS	2	(1)	1	(<1)	1	(1)
CHOLESTASIS	1	(<1)	0		1	(1)
HYPERBILIRUBINAEMIA	1	(<1)	1	(<1)	0	
INFECTIONS AND INFESTATIONS	2	(1)	1	(<1)	1	(1)
PULMONARY MYCOSIS	2	(1)	1	(<1)	1	(1)
INVESTIGATIONS	4	(2)	2	(1)	1	(1)
ALANINE AMINOTRANSFERASE INCREASED	1	(<1)	0		1	(1)
ASPARTATE AMINOTRANSFERASE INCREASED	1	(<1)	0		1	(1)
BLOOD ALKALINE PHOSPHATASE INCREASED	1	(<1)	0		1	(1)
ELECTROCARDIOGRAM QT PROLONGED	1	(<1)	1	(<1)	0	
GAMMA- GLUTAMYLTRANSFERASE INCREASED	1	(<1)	0		1	(1)
HEPATIC ENZYME INCREASED	1	(<1)	1	(<1)	0	
IMMUNOSUPPRESSANT DRUG LEVEL INCREASED	1	(<1)	0		0	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2	(1)	2	(1)	0	
RASH	2	(1)	2	(1)	0	

Adverse experiences are presented in decreasing frequency based upon the counts for all treatments combined.

Analysis of Quartile Exposure Data as it Relates to Adverse Experiences

A total of 64 subjects were included in the analysis of the incidence of adverse experiences by quartile of exposure.

Table 27.

	Cavg Mean (ng/mL)	Cavg Range	No. of Subjects	No. of Subject Reporting Any Treatment-Related Adverse Experience
Quartile 1	768 ng/mL	550 ng/mL to 1008 ng/mL	16	2 (13)
Quartile 2	1250 ng/mL	1048 ng/mL to 1394 ng/mL	16	6 (38)
Quartile 3	1528 ng/mL	1414 ng/mL to 1712 ng/mL	16	4 (25)
Quartile 4	2163 ng/mL	1721 ng/mL to 3034 ng/mL	16	4 (25)

Adverse events of special interest

Renal Adverse Events

There were no TEAEs related to renal function reported for the subjects in the 200 mg multiple dose group (Cohort 1).

Overall, a total of 15 subjects (6%) reported TEAEs related to renal function. Of these, 11 subjects (5%) reported TEAEs related to renal safety with an onset during the IV phase. The TEAEs related to renal safety with an onset during the IV phase reported by more than one subject were renal failure (3 subjects) and acute renal failure (7 subjects).

Of the 11 subjects reporting TEAEs related to renal safety with an onset during the IV phase, only two subjects (1%) with renal failure were determined by the investigator to be treatment related.

Vascular Adverse Experiences and Local Site Reactions

There was no TEAEs related to vascular function in the 200 mg dose group. The TEAE of pulmonary embolism with an onset during the IV phase was reported for one subject (Subject No. 4/000113):

> Subject No. 4/000113 is a 57-year-old white male with a history of AML who was diagnosed on Day 3 with candidemia (unresolved). On Day 4, he was diagnosed with Enterococcus faecium bacteremia (unresolved). The subject died on Day 24. Macroscopic exam of autopsy showed a massive intrapulmonary hemorrhage, suspected bilateral embolism of arteria pulmonalis and disseminated aspergillosis. The subject stopped study medication on Day 5. His Day 3 POS concentration was 1080 ng/mL. The investigator considered the events of "massive intrapulmonary hemorrhage, suspected bilateral embolism and disseminated aspergillosis" unlikely related to treatment with study medication.

One subject received (in violation of the protocol) nine consecutive days of POS IV solution via a peripheral line. This subject had several reported adverse experiences of thrombophlebitis.

Overall, 32 subjects (14%) reported TEAEs related to embolic and vascular function. Of these, 24 subjects (10%) reported TEAEs related to embolic and vascular function with an onset during the IV phase. One subject experienced subclavian vein thrombosis during the follow-up period, which the investigator assessed as unlikely related to study drug

With regard to local tolerability in subjects that received IV POS solution via a peripheral line, there were 9 subjects who received single doses of POS IV solution via a peripheral line. Of these, only one subject reported a local tolerability reaction (moderate pain at the peripheral catheter site, deemed unlikely related to study drug).

Table 28.

	Cohort 2/ Cohort 3 IV 300mg **TOTAL** n=237				Cohort 2/ Cohort 3 IV 300mg **IV Phase** n=237			
	All		Severe/LT		All		Severe/LT	
SUBJECTS REPORTING ANY ADVERSE EXPERIENCE	32	(14)	6	(3)	24	(10)	6	(3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3	(1)	3	(1)	3	(1)	3	(1)
ACUTE PULMONARY OEDEMA	1	(<1)	1	(<1)	1	(<1)	1	(<1)
ACUTE RESPIRATORY DISTRESS SYNDROME	1	(<1)	1	(<1)	1	(<1)	1	(<1)
ACUTE RESPIRATORY FAILURE	1	(<1)	1	(<1)	1	(<1)	1	(<1)
VASCULAR DISORDERS	30	(13)	3	(1)	22	(9)	3	(1)
HYPERTENSION	26	(11)	3	(1)	20	(8)	3	(1)
SUBCLAVIAN VEIN THROMBOSIS	1	(<1)	0		0		0	
VASCULAR OCCLUSION	4	(2)	0		3	(1)	0	

Hepatic Adverse Events

In cohort 1, one subject reported a TEAE of hyperbilirubinaemia with an onset during the IV phase. One subject reported a TEAE of jaundice with an onset during the Oral phase.

Overall, there were 9 subjects (4%) that reported TEAEs related to hepatic function. Of these, 7 subjects (3%) reported TEAEs related to hepatic function with an onset during the IV phase.

Table 29.

	Cohort 2/ Cohort 3 IV 300mg **TOTAL** n=237				Cohort 2/ Cohort 3 IV 300mg **IV Phase** n=237				Cohort 2/ Cohort 3 IV 300mg **Oral Phase** n=170			
	All		Severe/LT		All		Severe/LT		All		Severe/LT	
SUBJECTS REPORTING ANY ADVERSE EXPERIENCE	9	(4)	5	(2)	7	(3)	4	(2)	2	(1)	1	(1)
HEPATOBILIARY DISORDERS	9	(4)	5	(2)	7	(3)	4	(2)	2	(1)	1	(1)
ACUTE HEPATIC FAILURE	1	(<1)	1	(<1)	0		0		1	(1)	1	(1)
DRUG-INDUCED LIVER INJURY	1	(<1)	1	(<1)	1	(<1)	1	(<1)	0		0	
HEPATIC FUNCTION ABNORMAL	2	(1)	1	(<1)	1	(<1)	1	(<1)	1	(1)	0	
HEPATOTOXICITY	1	(<1)	0		0		0		1	(1)	0	
HYPERBILIRUBINAEMIA	4	(2)	2	(1)	4	(2)	2	(1)	0		0	
JAUNDICE	1	(<1)	0		1	(<1)	0		0		0	

A comparison of the treatment related TEAEs demonstrates that within the range of Cmax levels that have been observed in the serial-PK evaluable population in the 300 mg dose group, there does not appear to be an association of higher POS Cmax concentrations with a higher incidence of specific TEAEs, though these analyses should be interpreted with caution given the small number of subjects in each quartile.

Table 30. Summary of Adverse events by Cmax Quartile, by Category, 300 mg dose group Serial PK-Evaluable Population in P05520 – Number (%) of Subjects

	Quartile 1 (1150-2080) ng/mL n=12		Quartile 2 (2200-2530) ng/mL n=12		Quartile 3 (2540-3240) ng/mL n=12		Quartile 4 (3250-12200) ng/mL n=13	
Category								
Treatment Emergent AE	12	(100)	12	(100)	12	(100)	13	(100)
Treatment-Related Treatment Emergent AE	3	(25)	7	(58)	3	(25)	2	(15)
Serious AE	2	(17)	3	(25)	4	(33)	2	(15)
Death	1	(8)	1	(8)	0	(0)	0	(0)
Severe/Life-Threatening Treatment Emergent AE	4	(33)	8	(67)	9	(75)	10	(77)
Study Drug Discontinuation due to AE	1	(8)	3	(25)	3	(25)	0	(0)

Laboratory findings

The majority of laboratory value changes were mild in severity and transient in nature, and returned to baseline after cessation of POS therapy. For ALK-P, ALT, AST, and total bilirubin, grade shits from Grade 0 at baseline and remained either at Grade 0-1 at baseline occurred in 3-6% of patients. During the IV phase of the study, the most common grade shift was in total bilirubin (14 subjects [6%]).

For the predefined metabolic function laboratory parameters of serum potassium and serum sodium levels, the most common grade shift observed was in hypokalemia, with 70 subjects (30%) having a shift

of two grades to Grade 2. The largest shifts that occurred were from Grade 0 to Grade 3 (21 subjects [9%]).

For the predefined drug toxicity laboratory parameter of creatinine, the largest grade shift that occurred was one grade (from Grade 0 to 1) in 12 subjects (5%).

Hepatic advserse effects (Hy's law)

The P05520 protocol prespecified criteria for significant hepatic effect according to Hy's law (ALT and/or AST ≥3x ULN with ALK-P ≤2x ULN and total bilirubin ≥2x ULN without evidence of biliary obstruction [or alternative explanation]).

There was one subject in Cohort 1, three subjects in Cohort 2 and four subjects in Cohort 3 who met the predefined criteria for hepatic effect (Hy's Law); however, each of these subjects had other reasons which could possibly explain the combination of increased transaminase and total bilirubin (e.g., sepsis, GVHD, or another drug capable of causing the observed injury).

ACTH testing

The mean baseline aldosterone levels pre- and post-stimulation (1 hour) were decrease during treatment with posaconazole as known from previous studies with other formulations. No observed electrolyte imbalances in potassium or sodium levels were attributed to changes in adrenal function.

2.6.1. Discussion on clinical safety

Adverse events, including SAEs and deaths, were commonly seen as it can be expected in this population.

Cohort 1 (200mg) differed from cohorts 2 and 3 (300mg) not only in the dose of IV POS solution, but also in the underlying disease as HSCT patients were only enrolled in cohort 3. The MAH considers that the safety profile for the 2 dose levels was similar, although overall treatment related AEs and serious AEs were more common with the 300mg dose than with 200mg. However, due to the very low numbers in the 200mg dose group, such comparisons are not meaningful.

The AE profile seen with IV POS solution 300mg in this population is reported to be similar to the pattern observed with the oral suspension. The most common treatment emergent adverse events (TEAEs) with an onset during the IV phase were diarrhoea, nausea, vomiting, rash and hypokalaemia. Treatment related SAEs were reported from 2 subjects (hyperbilirubinaemia and pulmonary mycosis). Overall during the IV phase, the frequencies of treatment-related TEAEs were slightly higher for AML/MDS subjects (36%) than in HSCT subjects (20%), in particular gastro-intestinal side effects which may be a reflection of the underlying conditions. Severe AEs were similar in frequency.

Taking exposure into account, it was observed that the incidence of treatment-related TEAEs was higher in subjects in the second, third, and fourth quartiles when compared to subjects in the first quartile, but the same in subjects in the third and fourth quartile. This observation does not confirm or rule out an association of increased toxicity with higher POS concentrations.

Comparisons between oral phase and IV phase show no clear differences, but due to differences in duration of exposure, possible delays in onset of AEs and a carry- over of the higher exposures from IV administration into the oral phase such comparisons have to be regarded with caution.

The MAH reports that the safety profile in the 105 subjects who received prolonged dosing with the 300 mg POS IV solution (≥10 consecutive days) to be similar to the safety profile for the entire 300 mg dose group. Safety data in patients receiving IV POS solution continuously for > 14 and in particular > 28 days are very limited.

The overall incidence of TEAEs related to renal safety, adrenal/metabolic safety, hepatic function, hypersensitivity reactions, cardiac function and gastrointestinal disorders, the incidence of those reported by subjects with an onset during the IV phase, and the incidence of those reported by subjects with an onset during the Oral phase are reported to be similar to those commonly reported with POS oral suspension.

Posaconazole is known to have hepatotoxic effects. Seven of the 9 reported hepatic TEAEs in the 300 mg dosing groups occurred during the IV phase, 4 of which were considered severe. A further exploration of the incidence and severity of hepatic events did not show an association with exposure, based on the limited case numbers available.

Several cases of Hy's law were observed, with reportedly similar frequency to the oral suspension. Two cases fulfilling Hy's law criteria here were considered possibly drug related by the investigators, and in the assessor's view an association is not likely but cannot be ruled out in the remaining cases, as may be expected in this population of patients with significant disease and frequent concurrent medication including hepatotoxic agents.

When combining the safety data of IV posaconazole with those of the recently approved tablet formulation (which resulted in similar exposures as the IV formulation) an association between higher POS concentration and a higher incidence of overall and treatment-related TEAEs was not observed. Treatment emergent adverse hepatic events were highest in the 4th quartile, while treatment related hepatic events were inconsistent.

Other changes in selected laboratory evaluations in subjects in P05520 and who received POS IV solution were reportedly similar to that seen in the prior prophylaxis studies with POS oral suspension.

The increased Cmax after intravenous administration has minimal effect on left ventricular ejection fraction in healthy volunteers, but may be more relevant in patients with pre-existing abnormalities in myocardial function. There were no new or unexpected findings regarding QTc changes. The quartile exposure analysis did not indicate an increase in adverse events, including ECG changes, with higher Cmax. ECGs were however not routinely performed at the time of Cmax and the number of patients available for evaluation was small.

The vehicle for IV POS solution, cyclodextrin (SBECD), has been associated with kidney toxicity in rat models. Eleven of 15 renal TEAS occurred during the IV phase of which 10 cases are reported as renal failure or acute renal failure, of which 2 were reported treatment related. There was no demonstrable increase in treatment related renal events with IV POS solution compared to the oral suspension.

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 the pivotal study for this intravenous solution was generally similar to the AEs seen with the oral suspension, except for infusion site reactions.

Further exploration of the safety data did not show any clear evidence for an increase of overall or specific adverse events with the intravenous solution, however this finding is based on uncontrolled safety data available from the single pivotal study P05520 enrolling a relatively small number of patients.

Local toxicity, which precludes (repeated) administration via peripheral lines, was infrequently reported with administration through a central line, although there is some remaining concern that local effects may be masked. Thromboembolic events, reported in some non-clinical studies, were not reported during the study. However such events, unless extensive, are very difficult to diagnose in patients. Mean and

median treatment duration with the intravenous solution was 11 and 9 days, respectively, ranging from 2- 28 days. In total 67 patients received more than 14 days of IV posaconazole. None of these figures necessarily represents continuous treatment periods.

2.6.2. Conclusions on the clinical safety

No clear increase in overall or specific treatment related adverse events is reported. The small numbers, lack of a control group and shorter duration of treatment makes the interpretation of the adverse events very difficult. Comparisons with other studies and the frequencies of adverse events recorded in the SmPC are problematic and firm conclusion cannot be drawn.

No major additional safety concerns have been identified for IV posaconazole solution, but data are limited and thromboembolic events are a potential risk. Injection site reactions preclude repeated peripheral administration, however administration of a single dose of IV POS solution via a peripheral line is considered acceptable in cases where a central line is temporarily unavailable. In view of the limited duration of exposure and limited longer term safety data, administration of intravenous posaconazole solution should be of limited duration, and a switch to oral formulation when the patient's conditions allows, should be recommended in the SmPC.

The additional on-going study (P069) in the treatment of IFI, using both the intravenous and the tablet formulation of posaconazole is expected to generate useful additional safety data, and the applicant has agreed to specifically address safety aspects.

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.

Risk Management Plan

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

The RMP could be acceptable provided an updated RMP and satisfactory responses to the list of outstanding issues in the CHMP AR and at the end of PRAC assessment report are submitted:

- If *in vitro* data to determine if the drug is a substrate and inhibitor of OATP1B1 and OATP1B3 cannot be provided, the applicant is requested to include a study showing a lack of interaction effect of OATP1B1 and OATP1B3 substrates and inhibitors as a post-authorisation measure in the pharmacovigilance plan.

- The CHMP endorsed this advice without changes.
- The applicant will implement the changes in the RMP as requested by PRAC.
- The CHMP endorsed this commitment for the update of Risk Management Plan version 11.2 with the following content:

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* • *General – Infusion site reactions after peripheral line infusion of intravenous posaconazole* • *Renal - Renal effects of cyclodextrin with intravenous infusion of posaconazole*
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 haemorrhage* • *Respiratory – Pulmonary haemorrhage* • *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)* • *General – Infusion site reactions after central line infusion of intravenous posaconazole* • *Surgical and Medical Procedures - Off Label Use of IV Formulation in Pediatrics*
Missing information	• *Experience in children* • *General - Posaconazole as a possible substrate and/or inhibitor of OATP1B1 and OATP1B3*

Pharmacovigilance plan

Areas Requiring Further Investigation	Proposed Routine and Additional Pharmacovigilance Activities	Objectives
Identified risk #1: Hepatobiliary disorders		
Elevated Liver Enzymes; Hepatotoxicity; Hepatic Failure; Hepatitis	Routine Pharmacovigilance and Close Monitoring: event-specific follow-up questionnaire to collect details of hepatic disease evaluation for reported cases of safety concern for identified risk #1	Identification of potential safety signals
Identified Risk #2: Coagulopathies/Thrombotic Microangiopathies		
Thrombotic thrombocytopenia purpura; Hemolytic uremic syndrome	Routine Pharmacovigilance and Close	Thrombotic thrombocytopenia purpura; Hemolytic uremic syndrome
Identified Risk #3: Cardiac disorders		
Torsades de pointe	Routine Pharmacovigilance and Close Monitoring: event-specific follow-up questionnaire to collect details of cardiac arrhythmia evaluation for reported cases	Identification of potential safety signals

Areas Requiring Further Investigation	Proposed Routine and Additional Pharmacovigilance Activities	Objectives
	of safety concern for identified risk #3	
Identified risk #4: General		
Drug Interaction	Routine Pharmacovigilance; Close Monitoring; and event-specific follow- up questionnaire to collect details of drug interaction for reported safety concerns for identified risk #4.	Identification of potential safety signals
Identified risk #5: General		
Infusion site reaction after peripheral line infusion of intravenous posaconazole	Routine Pharmacovigilance	Identification of potential safety signals
Identified risk #6: Renal & Urinary disorders		
Renal effects of cyclodextrin with intravenous infusion of posaconazole	Routine Pharmacovigilance	Identification of potential safety signals
Potential risk #1: Blood dyscrasias		
Agranulocytosis; Aplastic anemia	Routine Pharmacovigilance and Close Monitoring: event-specific follow-up questionnaire to collect details of neutropenia/agranulocytosis evaluation for reported cases of safety concern	Agranulocytosis; Aplastic anemia
Potential risk #2: Cardiac disorders		
QTc prolongation; Heart failure; Myocardial infarction	Routine Pharmacovigilance and Close Monitoring: event-specific follow-up questionnaire to collect details of QT prolongation evaluation for reported cases of safety concern for potential risk #2	Identification of potential safety signals
Potential risk #3: Psychiatric disorders		
Depression; Suicide	Routine Pharmacovigilance	Identification of potential safety signals
Potential risk #4: Endocrine		
Adrenal insufficiency	Routine Pharmacovigilance and Close Monitoring: event-specific follow-up questionnaire to collect details of adrenal insufficiency evaluation for reported cases of safety concern for potential risk #4	Identification of potential safety signals
Potential risk #5: CNS		
Convulsion; Cerebral ischemia; Cerebral haemorrhage	Routine Pharmacovigilance and Close Monitoring: event-specific follow-up questionnaires to collect details of seizure/convulsion and cerebrovascular accident evaluation for reported cases of safety concern for potential risk #5	Identification of potential safety signals
Potential risk #6: Respiratory		
Pulmonary haemorrhage	Routine Pharmacovigilance and Close Monitoring	Identification of potential safety signals
Potential risk #7: Vascular		

Areas Requiring Further Investigation	Proposed Routine and Additional Pharmacovigilance Activities	Objectives
Hypertension	Routine Pharmacovigilance	Identification of potential safety signals
Venous thrombosis; Arterial thrombosis	Routine Pharmacovigilance and Close Monitoring: event-specific follow-up questionnaire to collect details of venous thromboembolic evaluation for reported cases of safety concern for potential risk #7	Identification of potential safety signals
Potential risk #8: Metabolism		
Hypokalemia	Routine Pharmacovigilance	Identification of potential safety signals
Potential risk #9: Neoplasms		
Occurrence of any neoplasm/malignancy, especially: Hepatic adenoma; Hepatic neoplasm; Adrenal adenoma; Adrenal neoplasm; Phaeochromocytoma	Routine Pharmacovigilance	Identification of potential safety signals
Potential risk #10: Infections		
Fungal infections	Routine Pharmacovigilance	Identification of potential safety signals
Potential risk #11 – Visual Effects		
Photopsia; Visual brightness; Visual disturbances	Routine Pharmacovigilance; and Close Monitoring	Identification of potential safety signals
Potential Risk #12 – Injury, Poisoning, and Procedural Complications		
Medication Error Related to Potential Substitution Between Different Formulations of Posaconazole (Tablet and Oral Suspension)	Routine Pharmacovigilance	Identification of potential safety signals
Potential Risk # 13 - General		
Infusion site reactions after central line infusion of intravenous posaconazole	Routine Pharmacovigilance	Identification of potential safety signals
Potential Risk # 14 Surgical and Medical Procedures		
Off label use of IV formulation in Pediatrics	Routine Pharmacovigilance	Identification of potential safety signals
Missing Information #1: Experience in Children		
Experience in Children	A clinical program in pediatric subjects is underway	Identification of potential safety signals

Areas Requiring Further Investigation	Proposed Routine and Additional Pharmacovigilance Activities	Objectives
Missing Information #2: General		
Posaconazole as a possible substrate and/or inhibitor of OATP1B1 and OATP1B3	An in vitro study is planned	Identification of potential drug-drug interactions

Ongoing and Planned Additional Pharmacovigilance Studies / Activities in the Pharmacovigilance Plan: Imposed Activities, Specific Obligations and Required Activities (Categories 1 - 3)

Study / Activity	Objectives	Safety Concerns Addressed	Status	Date for Submission of Interim / Final Reports (target dates)
In vitro investigation of posaconazole with the human hepatic uptake transporters OATP1B1 and OATP1B3	To evaluate whether POS is a substrate and/or inhibitor of OATP1B1 and OATP1B3			4Q2015

Risk minimisation measures

Summary of Safety Concerns and Risk Minimization Activities

SAFETY CONCERN	ROUTINE RISK MINIMIZATION MEASURES	ADDITIONAL RISK MINIMIZATION MEASURES
Important Identified Risks		
Hepatobiliary disorders – Elevated Liver Enzymes; Hepatotoxicity; Hepatic Failure; Hepatitis	Communication via professional and patient product information Listed under SmPC Section 4.4 (Special precautions and warnings for use) Package leaflet – Section 2, What you need to know before you use Noxafil; Section 4, Possible side effects	None
Coagulopathies/Thrombotic Microangiopathies – Thrombotic thrombocytopenic purpura; Hemolytic uremic syndrome	Communication via professional and patient product information Listed under SmPC Section 4.8 (Undesirable effects) Package leaflet- Section 4, Possible side effects	None
Cardiac disorders - Torsades de pointes	Communication via professional and patient product information Listed under SmPC Section 4.8 (Undesirable effects) Package leaflet – Section 2, What you need to know before you use Noxafil; Section 4, Possible side effects	None
General – Drug Interactions	Communication via professional and patient product information	None

Summary of Safety Concerns and Risk Minimization Activities

SAFETY CONCERN	ROUTINE RISK MINIMIZATION MEASURES	ADDITIONAL RISK MINIMIZATION MEASURES
	Listed under SmPC Sections 4.3, 4.4 and 4.5 Package leaflet – Section 2, What you need to know before you use Noxafil; Section 4, Possible side effects	
General - Infusion site reactions after peripheral line infusion of intravenous posaconazole	Communication via professional and patient product information Listed under SmPC Sections 4.2 (Posology and method of administration); 4.8 (Undersirable effects); 6.6 (Special precautions for disposal and other handling) Package leaflet – Section 4, Possible side effects and Informaton for medical or healthcare professionals	None
Renal & Urinary disorders - Renal effects of cyclodextrin with intravenous infusion of posaconazole	Communication via professional and patient product information Listed under SmPC Sections 4.2 (Posology and method of administration) and 5.2 (Pharmacokinetics in special populations) Package leaflet – Section 4, possible side effects	None
Important Potential Risks		
Blood dyscrasias – Agranulocytosis; Aplastic anemia	None	None
Cardiac disorders – QTc prolongation	Communication via professional and patient product information Listed under SmPC Section 4.4 (Special warnings and precautions for use) Package leaflet.-Section 2, What you need to know before you use Noxafil; Section 4 – Possible side effects	None
Cardiac disorders –Heart Failure; Myocardial Infarction	Communication via professional and patient product information Listed under SmPC Section 4.8 (Undesirable effects) Package leaflet – Section 2, What you need to know before you use Noxafil; Section 4, Possible Side effects	None
Psychiatric disorders – Depression; Suicide	Communication via professional and patient product information Listed under SmPC Section 4.8 (Undesirable effects) Package leaflet – Section 2, What you need to know before you use Noxafil; Section 4, Possible Side effects	None
Endocrine disorders – Adrenal Insufficiency	Communication via professional and patient product information Listed under SmPC Section 4.8 (Undesirable effects) Package leaflet – Section 4, Possible side effects	None
CNS disorders –	Communication via professional and patient product	None

Summary of Safety Concerns and Risk Minimization Activities

SAFETY CONCERN	ROUTINE RISK MINIMIZATION MEASURES	ADDITIONAL RISK MINIMIZATION MEASURES
Convulsion; Cerebral ischemia; Cerebral haemorrhage	information Listed under SmPC Section 4.8 (Undesirable effects) Package leaflet – Section 4, Possible side effects	
Respiratory disorders –Pulmonary haemorrhage	None	None
Vascular disorders – Arterial thrombosis; Venous thrombosis; Hypertension	Communication via professional and patient product information Listed under SmPC Sections 4.4 (Warnings and Precautions) and 4.8 (Undesirable effects) and 5.3 (Preclinical safety data) Package leaflet – Section 4, Possible side effects	None
Metabolism disorders - Hypokalemia	Communication via professional and patient product information Listed under SmPC Section 4.8 (Undesirable effects) Package leaflet –Section 2, What you need to know before you use Noxafil, Section 4, Possible side effects	None
Neoplasms – Occurrence of any neoplasm/malignancy, especially; Hepatic adenoma; Hepatic neoplasm; Adrenal adenoma; Adrenal neoplasm; Phaeochromocytoma	None	None
Infections – Fungal infections	Communication via professional and patient product information Listed under SmPC Section 4.2 (Posology and method of administration) Section 4.5Interaction with other medicinal products and other forms of interaction; and 5.1 Pharmacodynamic properties Package leaflet-Section1, What Noxafil is and what it is used for	None
Visual disorders – Photopsia; Visual brightness; Visual disturbances	Communication via professional and patient product information Listed under SmPC Section 4.8 (Undesirable effects) Package leaflet – Section 4, Possible side effects	None
Injury, Poisoning, and Procedural Complications – Medication Error Related to Potential Substitution between Different Formulations of Posaconazole (Tablet and Oral Suspension)	Communicated through Product and Package Design and Product Labeling	None
General – Infusion site reactions after central line infusion of intravenous posaconazole	Communication via professional and patient product information Listed under SmPC Sections 4.2, 4.8, and 6.6	None

Summary of Safety Concerns and Risk Minimization Activities

SAFETY CONCERN	ROUTINE RISK MINIMIZATION MEASURES	ADDITIONAL RISK MINIMIZATION MEASURES
	Package leaflet – Information for medical or healthcare professionals	
Surgical and Medical Procedures- Off Label Use of IV Formulation in Pediatrics	Communication via professional product information Listed under SmPC Section 4.2 (Posology and method of administration)	None
Missing Information		
Experience in Children	Communication via professional and patient product information Listed under SmPC Section 4.2 (Posology and method of administration) and and 5.2 (Pharmacokinetic properties) Package leaflet –Section 2, What you need to know before you use Noxafil	None
Posaconazole as a possible substrate and/or inhibitor of OATP1B1 and OATP1B3	None	None

2.8. Benefit Risk Balance

Benefits

- Beneficial effects

  The proposed intravenous formulation provides a means to administer posaconazole as a prophylactic and therapeutic agent in a situation where patients cannot take any oral medication at all or are unable to comply with the dietary requirement allowing the oral suspension to be absorbed to a satisfactory degree. When given as a single daily dose of 300 mg (administered through a central line), mean posaconazole exposure from the intravenous solution is higher than seen in previous studies with the oral suspension, given as a total daily dose of 600-800 mg in divided doses in the 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 vast majority of patients is expected to achieve Cavg concentrations > 500 ng/ml, which may be associated with positive clinical outcome. While a trend for better outcomes with higher exposures seems plausible, a clear threshold has not been identified.

  Pharmacokinetics 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. Data presented do not suggest that exposure in the treatment population is expected to be different from the prophylaxis population.

The observed data (serial PK evaluable patients) for both the 200 mg and 300 mg dose met the predefined exposure target for Cavg. The simulated data show that a higher proportion of subjects meet the exposure target with the 200 mg dose, with only a small increase of those below the target compared to the 300 mg dose. The 300 mg dose results in a greater proportion of patients with exposures beyond the upper target boundary. The applicant proposes the 300 mg dose based on the significantly higher number of patients expected to have a Cmin < 500ng/ml with the 200 mg dose, although Cmin was not the primary bridging parameter. This approach was justified as more conservative, and by the lack of an observed increase of adverse events from higher exposures based on data available so far.

Risks

- Unfavourable effects

  The safety profile for posaconazole has been established for the oral formulation and includes hepatotoxicity and QT prolongation. The most common treatment-related adverse events during treatment with the IV solution were diarrhoea, nausea, vomiting, rash and hypokalaemia. Hepatotoxic effects and QT prolongation were observed. In addition, the IV solution causes local reactions (thrombophlebitis).

- Uncertainty in the knowledge about the unfavourable effects.

  The model derived simulated data indicate that around 15% of patients are expected to exceed plasma concentrations of 2500 ng/ml including 3% who are expected to exceed the upper limit of 3650 ng/ml. As exposures exceed the levels achieved in previous studies there are limited safety data for exposures > 2500 ng/ml.

  There was no reported increase in overall or specific adverse events, including hepatic events, with at higher exposures obtained with the intravenous formulation, however safety data are very limited and further affected by the lack of a control group and the short duration of treatment. Safety data from patients with exposures> 2500 and > 3750 ng/ml are sparse. No significant effect of the higher Cmax resulting from intravenous formulation on QT was observed, however no ECG data around the time of Cmax were collected in patients. It is noted that the applicant will generate such data in the on-going phase III trial (PN069). Mild transient decrease of echocardiographically determined left ventricular ejection fraction may be correlated to Cmax in healthy volunteers, and may be more relevant in patients with myocardial impairment.

  Thromboembolic events were reported from non-clinical studies, while thrombophlebitis has been a concern with peripheral administration and may occur after central intravenous administration. No thromboembolic events were observed in patients, but are still considered a potential risk. It is reflected adequately in the RMP.

  The anticipated shorter duration of continuous treatment or prophylaxis expected with this intravenous solution may be relevant when evaluating safety concerns.

Benefit-Risk Balance

The benefit-risk balance for Noxafil 300mg concentrate for solution for infusion is considered positive in the proposed dose.

2.8.1. Discussion on the benefit-risk balance

The potentially greater risk of adverse events at the higher dose level of 300 mg has to be weighed against the risk of reduced efficacy with the 200 mg dose. Taking the lack of a documented exposure-effect relationship in the tested exposure range into account, the CHMP considers that the applicant's choice of dose is acceptable. It is further taken into account that the reported and simulated plasma concentrations after 300 mg of the intravenous formulation so far are no higher than those for the 300 mg gastro-resistant tablet formulation. Further PK and exposure data from the on-going Phase III study (PN069) in the treatment of IFI are expected. Additional safety and efficacy data are also expected in the foreseeable future from this study in the treatment of invasive fungal infections, with voriconazole as active comparator.

The benefit-risk balance for Noxafil 300mg concentrate for solution for infusion is considered positive iin the conditions of use detailed in the product information.

2.8.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate whether posaconazole is a substrate and/or inhibitor of the human hepatic uptake transporters OATP1B1 and OATP1B3.

No additional risk minimisation activities were required beyond those included in the product information.

2.9. Recommendation

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 300 mg concentrate for solution for infusion in the treatment of the following fungal infections in adults:

- 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 product subject to restricted medical prescription. (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.