11 November 2021
EMA/702418/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Noxafil

International non-proprietary name: posaconazole

Procedure No. EMEA/H/C/000610/X/0063/G

Note

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

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List of abbreviations

AEs	Adverse events
ALT	Alanine aminotransferase
ASaT	All Subjects as Treated
AST	aspartate aminotransferase
AUC	area under the curve
BID	Twice a day
Cavg	Average plasma concentration over the dosing interval at steady state
CSR	Clinical study report
DDI	drug-drug interaction
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EC	Esophageal candidiasis
EU	European Union
FDA	Food and Drug Administration
GVHD	Graft-versus-host disease
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplant
ICH	International Council for Harmonization
IFI	Invasive fungal infection(s)
ISE	Integrated Summary of Efficacy
IV	Intravenous
NCA	noncompartmental analysis
OS	Oral suspension
PD	pharmacodynamic(s)
PDCO	Paediatric Development Committee (of the EMA)
PFS	Powder for oral suspension
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
POS	Posaconazole
PSUR	Periodic Safety Update Report
QD	Once a day
QTc	QT interval corrected for rate
SAE	serious adverse event
TID	Three times a day
US	United States
Vc	Central volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

Merck Sharp & Dohme B.V. submitted on 14 September 2020 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

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

Extension application to introduce a new pharmaceutical form (gastro-resistant powder and solvent for oral suspension), grouped with a type II variation (C.I.6.a) to extend the approved indications for Noxafil to the paediatric population.

As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC, as well as the package leaflet, are updated.
The RMP (version 17.1) is updated in accordance.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

- Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

- Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008 - Extensions of marketing authorisations

This is a group of variations in accordance with Article 7.2 (b) of the Commission Regulation (EC) No 1234/2008 consisting of an Extension Application for Noxafil (posaconazole, EMEA/H/C/0610) to support the registration of a 300 mg gastro-resistant powder and solvent for oral suspension (PFS hereafter), a new age-appropriate oral formulation, and a Type II variation application (cat. C.I.6 a - Modification of an approved therapeutic indication) to extend the approved indications for Noxafil to the paediatric population.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0101/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/0101/2020 was not yet completed as some measures were deferred.

The PDCO issued an opinion on compliance for the PIP (EMEA-C2-000468-PIP02-12-M06).

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Christophe Focke

The application was received by the EMA on	14 September 2020
The procedure started on	26 November 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 February 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 February 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	16 February 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 March 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	21 May 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 July 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	22 July 2021
The MAH submitted the responses to the CHMP List of Outstanding Issues on	12 October 2021
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	27 October 2021
The outstanding issues were addressed by the MAH during an oral explanation before the CHMP during the meeting on	N/A

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 on	11 November 2021
The CHMP adopted a report on the similarity of Noxafil with isavuconazonium sulfate on (see Appendix on similarity)	22 July 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Invasive fungal infection (IFI) is a leading cause of infectious disease morbidity and mortality in immunocompromised patients, especially in those considered at high risk for severe and prolonged neutropenia or those who have received HSCT. As in adults, the paediatric patients at risk for developing IFI, primarily due to neutropenia and T-cell dysfunction, include, but are not limited to, allogeneic stem cell transplant recipients, and patients with acute leukemias, myelodysplasia, severe aplastic anemia, and advanced-stage non-Hodgkin lymphoma. The most common IFI in these immunocompromised children are aspergillosis, candidiasis and mucormycosis.

2.1.2. Epidemiology

The incidence of IFI in paediatric patients ranges from <5% to 10%, depending on patient-related risk factors and pathogenic characteristics. Although a number of agents are approved for the prophylaxis and treatment of IFI in both adults and children, mortality remains as high as 20% in patients who develop IFI. Given the high morbidity and mortality of IFI in high-risk paediatric patients, antifungal agents for prophylaxis and salvage treatment of IFI are warranted.

2.1.3. Clinical presentation, diagnosis

Recognizing an IFI can be difficult, because nonspecific clinical signs and symptoms or isolated fever are frequently the only presenting features. Therefore, a high index of clinical suspicion is necessary in patients at increased risk of IFI, which requires knowledge of the paediatric patient population at risk, additional predisposing factors within this population, and the clinical signs and symptoms of IFI.

The diagnosis of proven IFI can only be made by cultures obtained by sterile procedure or histopathologic, cytopathologic or direct microscopic evaluation of tissue specimens. However, tissue specimens are sometimes hard to obtain in patients receiving treatment for hematologic malignancies and HSCT patients due to thrombocytopenia and the potential risk of bleeding complications. Moreover, cultural-based methods have low sensitivity and specificity and are time consuming. Therefore, other diagnostic tools (radiologic, serologic and molecular methods) may be used for the diagnosis of IFI.

2.1.4. Management

In contrast to adults, detailed information of PK and/or PD of many antifungal agents is lacking in paediatric patients, and antifungal agents that have demonstrated effectiveness in adults have not

been licensed for use in paediatric patients. Few antifungal agents are approved for antifungal prophylaxis in children. However, given the need for managing IFI in paediatric patients, many antifungal agents in multiple classes are currently used for IFI prophylaxis and treatment in these patients. These include triazoles (fluconazole, itraconazole, posaconazole and voriconazole), lipid amphotericin B, and echinocandins (caspofungin and micafungin), each with their own benefits and risks. The choice of antifungal prophylaxis for paediatric patients is limited by side effects profiles, drug-drug interactions and PK characteristics. More agents and studies on existing agents are needed to meet the need of individualized care of the diverse patient populations at risk of developing IFI.

Currently approved antifungals for IFI prophylaxis in paediatric patients:

Treatment	**Indication**	**Formulation**
Mycafungin (EU MAA)	Neonates and children: Prophylaxis of candidiasis in patients undergoing allogeneic HSCT or patients who are expected to have neutropenia for 10 or more days.	Concentrate for solution for infusion
Fluconazole	Neonates and children: Prophylaxis of candidiasis in immunocompromised patients; cryptococcal meningitis.	Capsules, Powder for oral suspension, Solution for infusion
Voriconazole (EU MAA)	Children ≥2 years old: Prophylaxis of invasive fungal infections in high risk allogeneic HSCT recipients.	Tablets, Powder for oral suspension, Powder for solution for infusion

Currently approved antifungals for IFI treatment in paediatric patients:

Treatment	**Indication**	**Formulation**
Liposomal Amphotericin B	Neonates and children: Treatment of invasive aspergillosis in patients refractory or intolerant to voriconazole; candidiasis and cryptococcal meningitis; empiric treatment for patients with febrile neutropenia.	Powder for solution for infusion
Caspofungin (EU MAA)	Children ≥1 year old: Treatment of invasive candidiasis; invasive aspergillosis in patients refractory to or intolerant of amphotericin B, lipid formulations of amphotericin B and/or itraconazole; empiric treatment for patients with febrile neutropenia.	Powder for solution for infusion
Mycafungin (EU MAA)	Neonates and children: Treatment of invasive candidiasis.	Concentrate for solution for infusion
Fluconazole	Neonates and children: Treatment of candidiasis; cryptococcal meningitis.	Capsules, Powder for oral suspension, Solution for infusion
Voriconazole (EU MAA)	Children ≥2 years old: Treatment of invasive aspergillosis; candidaemia in non-neutropenic patients; fluconazole-resistant serious invasive Candida infections; serious fungal	Tablets, Powder for oral suspension, Powder for solution for infusion

	infections caused by Scedosporium spp. and Fusarium spp.	

2.2. About the product

Posaconazole is a broad-spectrum triazole antifungal compound which exhibits potent antifungal activity against a variety of yeasts and molds (*Aspergillus* species, *Candida* species, *Coccidioides immitis*, *Fonsecaea pedrosoi*, and species of *Fusarium, Rhizomucor*, *Mucor*, and *Rhizopus)*, including strains resistant to amphotericin B and other triazoles. Posaconazole, like other azoles, blocks the synthesis of ergosterol, a key component of the fungal membrane, through the inhibition of the enzyme lanosterol 14α–demethylase (CYP51).

Posaconazole 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;

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

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

- Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (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.

2.3. Type of Application and aspects on development

The development of an age-appropriate formulation and studies P032 and P097 are part of the currently agreed paediatric investigation plan and have been agreed with the PDCO.

2.4. Quality aspects

2.4.1. Introduction

Noxafil 40 mg/ml oral suspension and Noxafil 100 and 300 mg gastro-resistant tablets are already authorised medicinal products in the EU (EU/1/05/320/001-004). This is a line extension to register a new pharmaceutical form (gastro-resistant powder and solvent for oral suspension).

The finished product is presented as gastro-resistant powder and solvent for oral suspension containing 300 mg of posaconazole as active substance.

Other ingredients are:

Powder: Hypromellose acetate succinate

Solvent: purified water, glycerol (E 422), methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate, sodium dihydrogen phosphate monohydrate, citric acid anhydrous (E 330), xanthan gum (E 415), sodium citrate (E 331), saccharin sodium (E 954), microcrystalline cellulose, carmellose sodium, carrageenan calcium sulfate trisodium phosphate (E 407), sorbitol solution (E 420), potassium sorbate (E 202), flavour berry citrus sweet containing propylene glycol (E1520), water, natural and artificial flavour, antifoam Af emulsion containing polyethylene glycol (E1521), octamethyl cyclotetrasiloxane, and decamethylcyclopentasiloxane and poly(oxy-1,2-ethanediyl), alpha-(1-oxooctadecyl)-omega-hydroxy.

The finished product gastro-resistant powder and solvent for oral suspension is supplied as a pack containing:

Package 1: The kit contains 8 child-resistant single-use sachets (PET/aluminium/LLDPE), two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, one 473 mL solvent bottle (HDPE) with polypropylene (PP) closure with a foil induction seal liner, and one bottle adapter for the solvent bottle.

Package 2: A box of six 3 mL (green) and six 10 mL (blue) notched tip syringes.

Package 1 and 2 are provided together as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The active substance used to manufacture the new pharmaceutical form gastro-resistant powder and solvent for oral suspension is the same as that used in the manufacture of the currently authorised 40 mg/ml oral suspension and 100 and 300 mg gastro-resistant tablets (EU/1/05/320/001-004). The information presented by the applicant in the dossier was already assessed in the original submission and includes updates from any subsequent variations. The active substance is sourced from the same manufacturer, is manufactured by the same process, it is released in accordance with the same active substance specification and has the same retest time.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as gastro-resistant powder in single use sachets and solvent for oral suspension containing 300 mg of posaconazole as active substance. The powder is co-packaged with a suspending vehicle, devices and ancillary components as described in in section 6.5 of the SmPC.

Prior to dosing, the powder is dispersed in 9 mL of suspending vehicle to obtain 10 mL total of suspension with a final concentration of approximately 30 mg/mL. The intended commercial finished product is a pH-controlled delayed release/gastro-resistant formulation containing amorphous posaconazole in a solid dispersion powder.

The pharmaceutical form, Posaconazole PFS, subject to this line extension was developed for the paediatric population 2 to 18 years of age with the scope to avoid the food effect observed with the oral suspension formulation, but not observed with the tablet formulation.

Powder

The powder for oral suspension (PFS) is supplied as an off-white to yellow powder in sachets.

The active substance used in the development and manufacture of powder for oral suspension is identical to that used in the marketed products tablet and oral suspension.

The PFS formulation developed using the same key functional component used in the approved marketed tablet formulation, which does not present food interaction. The excipient HPMCAS is a well-known pharmaceutical ingredient, also used in the tablet formulation, and its quality is compliant with USP-NF 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 and in paragraph 2.1.1 of this report.

Principles consistent with ICH Q8, Q9, and Q10 were used during development, including a quality target product profile (QTPP), to guide development, the use of quality risk management, process analytical technology tools and risk-based development studies across scales. The proposed control strategy for posaconazole PFS consists of process parameters, proven acceptable ranges in-process controls and release specifications. However, no design space was claimed.

The powder is sacheted and co-packaged with a suspending vehicle and the ancillary components to produce the final product.

The sachet packaging operation, the posaconazole powder is filled into foil sachets.

The primary packaging is child-resistant single-use sachets (PET/aluminium/LLDPE). The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Suspending vehicle

The suspending vehicle used with the powder for oral suspension (PFS) is a cloudy, colourless liquid.The suspending vehicle (9 mL) is used to disperse Posaconazole PFS to obtain 10 mL total of suspension with a final concentration of approximately 30 mg/mL.

The excipients used in the manufacture of the suspending vehicle are the subjects of current monographs in the USP/NF and/or Ph. Eur. and are tested and meet the requirements found therein prior to use, as applicable. Excipients which are not the subject of any compendial monographs meet the requirements of the in-house specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The levels of the excipients in the suspending vehicle are well below acceptable daily intake (ADI) amounts.

finished product constituted with the suspending vehicle is considered safe at the proposed levels of preservatives for the intended paediatric population.

The primary packaging is HDPE oval bottle, a polypropylene closure with a foil induction seal liner inside the cap, is used to seal the bottle closed. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Posaconazole PFS is supplied with medical devices and ancillary devices, all of them are CE marked:

- Package 1: The kit contains 8 child-resistant single-use sachets (PET/aluminium/LLDPE), two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, one 473 mL solvent bottle (HDPE) with polypropylene (PP) closure with a foil induction seal liner, and one bottle adapter for the solvent bottle.
- Package 2: A box of six 3 mL (green) and six 10 mL (blue) notched tip syringes.

The notch-tip syringe provided in the kit should be used to administer Noxafil with the enteral feeding tube. The enteral feeding tube size should be selected based on the patient characteristics.

Compatibility and in-use testing have demonstrated acceptable compatibility with both the mixing cup and oral syringes used.

Manufacture of the product and process controls

Powder

The manufacturing process consists of 3 main steps, following by sachet packaging and co-packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Suspending vehicle

The manufacturing process consists of 2 main steps. The blended solution is then filled into bottles. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

Powder

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (HPLC) and microbiological quality (Ph. Eur.).
The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed in response to a MO, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 4 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Suspending vehicle

The finished product release include appropriate tests for this kind of product: description (visual), identification-preservatives (HPLC), assay-preservatives (HPLC), pH (Ph. Eur.), specific gravity (USP), microbiological enumeration tests (Ph. Eur.)

The finished product shelf-life specifications include appropriate tests: description (visual), pH (Ph. Eur.), container weight change (USP), assay- preservatives (HPLC) and viscosity (viscosity)

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impuritiesdemonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested as Major Objection (MO)) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 4 commercial scale clinical and stability batches, as well as 3 development commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Powder

Stability data from 3 commercial batches of finished product stored for up to 36 months under long term conditions (30 °C / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing

Samples were tested for description, assay, degradation products, dissolution,water activity, crystallinity by x-ray powder diffraction, in-use test and microbiological quality. In addition, identity and uniformity

of dosage units by weight variation were performed. The analytical procedures used are stability indicating.

In-use stability was assessed The data supports the length of the proposed in use period is 30 minutes (SmPC section 6.3).

A bulk hold time (BHT) study was designed to evaluate the stability of the powder in the bulk containerNo significant changes were observedThe proposed bulk holding time is acceptable.Based on available stability data, the proposed shelf-life for the product is 2 years when stored at the proposed storage condition as stated in the SmPC section 6.3 and 6.4, are acceptable.

Suspending vehicle

The claimed shelf-life for the suspending vehicle is 24 months. Stability results for 4 commercial and 2 pilot scale batches have been presented at long-term and accelerated condition in support of the shelf-life claimed. Real time (24 months at 25 °C / 60% RH) data is available. Results for description, pH, and TAMC are conform to specifications

Stability data from 4 commercial and 2 pilot scale batches of the suspending vehicle stored for up to 24 months under long term conditions (25 °C / 60% RH) and for up to 3 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing

Samples were tested for description, pH, and TAMC are conform to specifications. The analytical procedures used are stability indicating.

An in-use shelf-life study was conducted Results showed no significant change.

Adventitious agents

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

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner for this new pharmaceutical form. 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 and their manufacturing process.

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.

Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

The approval of POS PFS is supported by the comprehensive non-clinical programmes conducted for the marketed POS oral suspension and IV solution formulations. These programmes established a data set to characterize the pharmacology, pharmacokinetics, and toxicology profile of POS. In addition, toxicology studies in neonatal/juvenile and young adult animals were completed with the marketed formulations, supporting the expanded indication of POS IV solution and the administration of POS PFS to a paediatric population ≥ 2 years of age. Therefore, additional non-clinical studies with POS PFS were not conducted.

The non-clinical module submitted by the MAH was limited to discussion of the studies conducted in neonatal/juvenile and young adult animals with POS oral suspension or POS IV solution, e.g.

- In juvenile rats: a dose-range finding and a pivotal 12-week toxicity studies conducted with the POS oral suspension (studies no. SN 07366, SN 07193). A second 12-week study was performed subsequently to clarify mammary gland and salivary gland findings (study no. SN 09005);

In juvenile dogs: a dose-range finding and a pivotal 9-month toxicity studies conducted with the POS oral suspension, as well as a pivotal 6-week study conducted with the POS IV solution (studies no. SN 07367, SN 07194, TT#12-9018). To clarify some concerns on the developing brain identified in the latter study, two additional 13-week studies were performed with the POS IV solution, one in juvenile dogs and the other in young adult animals (studies no. TT#14-1001 and TT#13-1062).

2.5.2. Pharmacology

No additional pharmacology studies were conducted to support paediatric indications for POS IV solution and POS PFS.

2.5.3. Pharmacokinetics

No additional pharmacokinetic studies were conducted with POS to support paediatric indications for POS IV solution and POS PFS.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single dose toxicity studies were submitted in support of the present application.

2.5.4.2. Repeat dose toxicity

No additional repeat-dose toxicity study was submitted.

To support a previous application for approval of POS as oral suspension, repeat-dose toxicity studies were conducted in mice for up to 3 months with oral doses up to 90 mg/kg, in rats for up to 6 months with oral doses up to 45 mg/kg, and in dogs for up to 1 year with oral doses up to 30 mg/kg. A 1-year neuropathology study was also conducted in monkeys. To support approval of POS IV solution, a 1-month study in monkeys with doses up to 12 mg/kg and a 3-month study in dogs with doses up to 9

mg/kg were performed. The latter dog study is the study no. TT#13-1062 discussed above. Below is a short summary of the main findings detailed in the EPAR.

In oral studies, treatment-related effects were reported in the adrenal glands of rats and dogs at exposure levels equal to or greater than those attained in humans (adrenal suppressive effects due to class-related inhibition of steroid hormone synthesis). Posaconazole was also shown to induce phospholipidosis in all species, where it was observed in several tissues as vacuolated macrophages (lungs), histiocytes (spleen, thymus, lymph nodes) and Kupffer cells (liver). Phospholipidosis in these tissues was not associated with functional effects, except pulmonary phospholipidosis in the 2-year carcinogenicity study in rats. In other species exposed to similar posaconazole levels, pulmonary phospholipidosis was less severe and not associated with overt functional changes. Moreover, phospholipidosis was observed in neural tissues of dogs only as vacuolation of neurons in the brain and Auerbach's plexus of the intestine and welling axons in the brain and spinal cord. A neurotoxicity study showed that this was not associated with functional changes in central and peripheral nervous systems. The highest dose at which neuronal phospholipidosis without functional effects were observed in dogs was 30 mg/kg, which represents animal to human exposure multiples of approximately 3 fold. It was concluded that neuronal phospholipidosis seen in dogs is unlikely to be of clinical significance considering also the absence of this finding and lack of functional effects in the 1-year monkey study.

In the 1-month intravenous monkey study, a non-dose related incidence of thrombus/emboli in the lung was seen.

2.5.4.3. Genotoxicity and Carcinogenicity

No additional studies were submitted.

Posaconazole showed no genotoxic potential in *in vitro* and *in vivo* studies. In long-term carcinogenicity studies conducted in rats at oral doses up to 30 mg/kg/day and in mice at oral doses up to 90 mg/kg/day, no finding indicative of a special hazard for humans was reported. Adrenal tumours were reported in rats as a consequence of a class effect of azole antifungals.

2.5.4.4. Fertility and early embryonic development, embryofoetal development, and pre and postnatal development

No additional studies were submitted.

DART studies conducted by the oral route to support the use of the previously approved oral suspension, and bridging studies conducted in rats and rabbits to support the IV formulation demonstrated similar exposure profiles via oral and IV route. Briefly, no effect was reported on male and female fertility in rats at up to 180 and 45 mg/kg (1.7-fold and 2.2-fold the human exposure). In embryo-foetal toxicity studies, there were increases in skeletal variations and malformations at subtherapeutic exposure levels in rats, and increases in resorptions and skeletal variations in rabbits; these effects were considered as related to azole-related effects on steroidogenesis. In the rat pre- and postnatal development study, dystocia, increased gestation length, reduced litter size and postnatal viability were observed with also foetal anomalies reported previously.

2.5.4.5. Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

2.5.4.5.1. Studies conducted in rats

Table 1: summary of toxicity studies in juvenile rats

Species **Study status** **Study ID / GLP**	**Route, duration, doses**	**Main findings**
Rat (SD) aged PND 7 24/sex/group DRF study SN 07366 GLP: Yes	Oral (gavage) 15 days (PND 7-21) 0, 25, 75, 150 mg/kg/day	• 25: ↓body weight (8.5%-9.0% on PND21), ↓body weight gain (11.5%-12.1% on PND 7-21) • ≥75: excessive toxicity incl. mortality from PND11 leading to premature termination of these groups on PND 13/14 (clin signs including abdominal distension, ↓activity, cold-to-touch, labored breathing, weakness, dehydration, tremors; 7/48 and 17/48 found dead or prematurely euthanised in moribund condition at 75 and 100 mg/kg), ↓body weight and body weight gain (based on a limited dataset), intestine (pale yellowish material or discoloration)
Rat (SD) aged PND 7 60/sex/group (main:15/sex/group; recovery: 15/sex/group; reproductive phase: 15/sex/group; TK: 15/sex/group) Pivotal study SN 07193 GLP: Yes	Oral (gavage) 12 weeks (PND 7-91) + 6 weeks recovery [Subgroup D (TK): PND 7-21] 0, 1, 5, 20 mg/kg/day	• ≥1: sexual maturation (dose-related ↓day of vaginal opening - within historical control range), hematology (transient ↓RBC count, hemoglobin, hematocrit and ↑MCV value; seen on PND42 only, not associated with ↑reticulocyte counts), **adrenal gland** (↑wt, cortical hypertrophy, vacuolation in zona fasciculata), **kidney** (tubular dilation), **mammary gland** (mammary adenocarcinoma in 1/15 F, described as subcutaneous masses at macroscopic examination from PND 68/69) • ≥5: **clinical observations** (masses in 2F at 5 mg/kg in ventral cervical/thoracic regions from PND 68/69), serum chemistry (↑cholesterol, ↑Na, ↓K, ↓Cl), urinalysis (dose-related ↑volume and ↓osmolality in F - reversible), **liver** (hepatocellular vacuolation), **mammary gland** (mammary adenocarcinoma in 1/15 F, described as subcutaneous masses at macroscopic examination from PND 68/69), **salivary gland** (carcinoma in 1/15 F) • 20: serum chemistry (↓ albumin, globulin, and total protein), urinalysis (↓specific gravity in F), **bone marrow** (hematopoietic hypercellularity), **lung** (macrophage accumulation), **heart** (↑wt, mixed cell infiltration in F), **kidney** (↑wt), **liver** (↑wt in F, inflammation), **ovary** (↑wt, interstitial cell vacuolation), **testis** (↑wt), **spleen** (↑wt, ↑extramedullary hematopoiesis), **bone** (slight ↓femoral width) <u>End of recovery</u> • ≥5: serum chemistry (↑Na in F), **adrenal gland** (angiectasis in F) • 20: **adrenal gland** (↑wt), **liver** (hepatocellular vacuolation - trend towards reversal), **testis** (↑wt)
Rat (SD) aged PND 7– 60/sex/group (48/sex/group + 12/sex/group for TK) Pivotal study SN 09005 GLP: Yes	Oral (gavage) 12 weeks (PND 7-91) [TK animals: PND 7-21] 0, 1, 5, 20 mg/kg/day	• ≥5: ↓body weight gain (PND 7-21), **adrenal gland** (enlarged, cortical hypertrophy, vacuolation in zona fasciculata) • 20: **testis** (↑wt), **epididymis** (↑wt), **kidney** (tubular dilation in F), **ovary** (interstitial cell vacuolation)

Table 2: toxicokinetic parameters in juvenile rat studies

Study	Time	Dose (mg/kg)	Cmax (ng/mL)		AUC (ng.h/mL)		Exposure multiple (AUC)*			
							2 to <7 years		7 to <7 years	
			M	F	M	F	M	F	M	F
JAS, rat SN 07193	PND21	1	246	205	3510	3130	0.2	0.1	0.1	0.1
		5	1570	1600	23700	22800	1.0	1.0	0.9	0.9
		20	6580	7090	108000	111000	4.7	4.8	4.3	4.4
JAS, rat SN 09005	PND21	1	269	303	4620	4300	0.2	0.2	0.2	0.2
		5	1730	1850	26000	25900	1.1	1.1	1.0	1.0
		20	7250	8230	141000	155000	6.1	6.7	5.6	6.2

*based on AUC0-24 levels of 23,000 and 25,000 ng.h/mL in children aged 2 to <7 years and 7 to 17 years, respectively, treated with posaconazole gastro-resistant powder and solvent for oral suspension (see SmPC 5.2)

a) <u>Dose Range Finding Oral (Gavage) Toxicity Study in the Neonatal Rat (SN 07366)</u>

This study was conducted to determine doses for the definitive study. The findings were consistent with those previously observed with POS in previous nonclinical studies, and there were no new POS-related toxicities identified. The NOAEL was < 25 mg/kg/day due to the effects on body weight gain observed at ≥ 25 mg/kg/day and moribund condition and mortality at ≥75 mg/kg/day.

b) <u>A Three-Month Oral (Gavage) Toxicity and Toxicokinetic Study in Neonatal and Juvenile Rats with a Six-Week Recovery Period (SN 07193)</u>

The objective of this study was to evaluate the potential effects of POS on growth, bone maturation, neurobehavioral and reproductive development when administered by oral gavage to rats daily for 12 weeks from PND 7 to 91. Four groups of 60 rats per sex were gavage daily with posaconazole doses of 0, 1, 5 or 20 mg/kg/day and assigned within each dose level to one of four subgroups (main study, recovery, reproductive or toxicokinetic) evaluating different parameters. Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, clinical pathology, organ weights, and gross and histopathological examination. Additionally, femoral bone measurements, behavioral performance (auditory startle, motor activity and water maze assessments) and reproductive parameters (estrous cycle, mating and fertility, reproductive function and development) were evaluated. Pups assigned to the TK subgroup were dosed from PND 7 to 21, with determination of drug plasma levels on PND 21.

There was no POS-related mortality, clinical signs or effects on body weight or food intake. A slight decrease in the day of vaginal opening was noted at 20 mg/kg/day, but the toxicological significance of this effect is uncertain since the value was within the historical control data range. There was no POS-related effect on any of the behavioral assessments, on fertility, reproductive function, or development of the F_2offspring.

Minimal transient decreases were observed on PND 42 in red blood cell count, hemoglobin and hematocrit for females and males at all dose levels that correlated with slightly increased mean corpuscular volume values but were not associated with an increase in reticulocyte counts. The changes observed in the red blood cell counts may have been associated with the microscopic findings (extramedullary hematopoiesis) observed in the spleen at terminal necropsy. There were mild increases in cholesterol levels observed in males at 20 mg/kg/day and females at 5 and 20 mg/kg/day on PND 42. A comparable increase in cholesterol levels was also observed at the end of the dosing period (PND 92) in males and females at 20 mg/kg/day. On PND 42, slight increases in sodium were observed in males at 5 and 20 mg/kg/day and females at 20 mg/kg/day. Females at 20 mg/kg/day also exhibited significantly lower potassium levels. On PND 92, males at 20 mg/kg/day and females at 5 and 20 mg/kg/day exhibited slight decreases in potassium and chloride levels. Minimal decreases in albumin and globulin levels resulted in slight decreases in total protein levels in males and females at 20 mg/kg/day. In addition, on PND 92, females at 20 mg/kg/day showed statistically higher levels of

sodium concentration. At the end of the dosing period (PND 90 and 91), a marked increase in urine volume in females was noted, with a corresponding decrease in urine specific gravity and osmolality at 20 mg/kg/day, in addition to a minimal increase in urine volume observed in females at 5 mg/kg/day, associated with a decreased osmolality. Following the recovery period (PND 134), no noteworthy differences in hematology, serum chemistry and urinalysis were noted as compared to controls, indicating recovery of these parameters.

Males and females administered 20 mg/kg/day exhibited a slight decrease in femur width when measured on PND 21/22. At the end of the dosing phase on PND 92, a decrease in femur width was observed only in females at 20 mg/kg/day. There were no POS-related differences in the femoral bone measurement (length and width) in the animals at the end of the recovery period.

At the end of the dosing phase, there was an increase in the weight of the adrenal glands in females at all dose levels and in males at ≥ 5 mg/kg/day. The weight of the pituitary gland was increased in females at all dose levels. Other POS-related differences in organ weights were seen in males and/or females at 20 mg/kg/day and consisted of increased kidney, heart, spleen, ovary, testis and liver (female only) weights. POS-related macroscopic changes were limited to enlargement of the adrenal glands of the males at 20 mg/kg/day and females at ≥ 5 mg/kg/day at the end of the dosing phase. There were no macroscopic observations attributed to the administration of POS in the animals assigned to the recovery subgroup in this study.

At the end of the dosing phase, POS-related microscopic findings were observed in adrenal glands of males and females at all dose levels (vacuolation: zona fasciculata and/or hypertrophy: cortical); in the liver (vacuolation: hepatocellular, inflammation) of males and/or females given ≥ 5 mg/kg/day as well as in the bone marrow (hypercellularity: hematopoietic), lung (macrophage accumulation), ovary (vacuolation: interstitial cell), heart (infiltration: mixed cell) and spleen (hematopoiesis/extramedullary: increased) of males and/or females at 20 mg/kg/day. In addition, minimal to slight renal tubular dilatation was noted in males and females at all dose levels. Microscopic findings with unclear toxicological/biological significance were present and consisted of mammary adenocarcinoma observed in one female at 1 mg/kg/kg and one female at 5 mg/kg/day and salivary gland carcinoma observed in one female at 5 mg/kg/day. No POS-related microscopic findings were noted in the bone of the animals assigned to the toxicokinetic study.

At the end of the 6-week recovery period, there remained a slight increase of the weight of the adrenal glands and testis at 20 mg/kg/day. In addition, following the recovery period, POS-related microscopic findings were observed only in the adrenal glands (angiectasis) of females at ≥ 5 mg/kg/day and in the liver (vacuolation: hepatocellular) of females at 20 mg/kg/day. While adrenal gland organ weights suggested at least partial recovery 6 weeks after the end of dosing, minimal to slight angiectasis was noted in females at ≥ 5mg/kg/day. Liver findings of hepatocellular vacuolation was considered minimal and showing a trend towards recovery. There was a complete reversal of the other POS-related microscopic findings described in the main study animals.

c) POS Oral Suspension: A 12-Week Oral (Gavage) Toxicity and Toxicokinetic Study of POS in Neonatal and Juvenile Rats (SN 09005)

The objective of this study was to evaluate the potential effects of POS on growth and morphological development of the mammary and salivary glands when administered orally at 0, 1, 5, and 20 mg/kg/day by gavage to rats (48/sex/group) for 12 weeks from PND 7 to 91. An assessment of toxicokinetics in 12 rats/sex/group dosed up to PND 21 was also conducted. Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, physical development (days to vaginal opening), organ weights (epididymides and testis), gross examination and

histopathologic examination (limited to salivary and mammary glands and tissues with macroscopic abnormalities).

There was no POS-related mortality. There were no toxicologically significant POS-related clinical signs or effects on the body weight or food intake values. No POS related changes were observed in days of development of vaginal opening.

An increase of the absolute testis and epididymis weight in males at 20 mg/kg/kg was noted. There was also an increasing trend of the absolute weight for the testis in males at 20 mg/kg/day. However, these observations at 20mg/kg were not considered biologically significant and were not considered adverse. Macroscopic observations attributed to the administration of POS were enlarged adrenal glands in males and females at ≥ 5 mg/kg/day.

There were no microscopic findings attributed to the administration of POS in the salivary glands or mammary glands examined. POS-related microscopic findings were observed in tissues showing macroscopic abnormalities and included cortical hypertrophy and/or vacuolation of the zona fasciculata in the adrenal glands (males and females at ≥ 5 mg/kg/day); tubular dilatation in the kidney (females at 20 mg/kg/day) and interstitial cell vacuolation in the ovary (females at 20 mg/kg/day). The findings in the adrenal glands, kidneys, and ovaries were consistent with findings in from the previous study in juvenile rats.

d) <u>Conclusion on juvenile rat studies</u>

In a definitive neonatal/juvenile rat study, POS oral suspension was administered at single daily oral (gavage) doses of 1, 5 or 20 mg/kg/day for 12 weeks from PND 7 to Day 91, followed by a 6-week recovery period (SN 07193). There was no new toxicity noted compared to adult rats and the results from this study were consistent with the known effects of POS and/or azole antifungals.

Mammary adenocarcinomas were observed at 1 mg/kg/day (1/15 females) and 5 mg/kg/day (1/15 females), and a salivary gland carcinoma was observed at 5 mg/kg/day (1/15 females). These observations were considered spurious and not related to the test article due to a lack of dose-response (not observed at the high dose level), inconsistency with existing carcinogenicity data, and considering the absence of histologic trend indicating neoplastic progression (no other main group or recovery animals had any proliferative, hyperplastic or hyper secretory activity of any organs). A second study in rats of the same age and using the same dose levels but with greater statistical power was conducted to assess potential effects on mammary and salivary glands (study no. SN 09005). Tumor findings were not replicated in this more extensive study.

The NOAEL in both neonatal/juvenile rat studies conducted with POS oral suspension was 1 mg/kg based on multiple histopathology findings consistent with existing data with POS in adult animals.

The CHMP considered that a 3-month study in rats was performed at doses of 5, 30 and 60 mg/kg/day as part of the initial MAA for Noxafil. The target organs reported at all dose levels were adrenal glands, bone marrow, Harderian gland, heart, liver, lung, ovaries, pituitary gland, spleen and examined lymphoid tissues. Bone effects were also observed at 30 and 60 mg/kg/day (fractures, thinning), and tooth findings (hypertrophy of the periodontal membrane) were seen at 60 mg/kg/day. The NOAEL had been determined at 5 mg/kg/day.

The findings reported in the new 12-week juvenile rat study are generally consistent with those observed in the 3-month repeat-dose toxicity study submitted to support the initial MAA of Noxafil. No additional target organ was identified. Of note, histopathological findings seen in ovaries and testes weight changes did not impact on the reproductive capacity of animals exposed to posaconazole. In addition, the slight bone effects (decrease width) seen at 20 mg/kg/day were reversible.

In the first juvenile study (SN 07193), mammary adenocarcinoma was reported in 1/15 females at each the low and mid dose level and corresponded to the subcutaneous masses detected at macroscopic examination after 8-9 weeks of dosing (from PND 68/69). In addition, a salivary gland carcinoma was observed in 1/15 female at the mid dose level. The relationship to treatment of these findings was considered as questionable due to the lack of dose-relationship (not seen in the high dose group), and considering also the absence of concern for genotoxicity and carcinogenicity from studies supporting the original approval of posaconazole. To further clarify this issue, a second 12-week study was conducted in rats of the same age treated at the same dose levels. It was focused on potential treatment-related effects on mammary and salivary glands, using a higher number of animals at histopathological examination (48/sex/group). No adverse effects attributable to posaconazole were observed in these tissues. Therefore, the MAH's position on this issue is considered as acceptable.

Overall, the toxicological profile of posaconazole appears as similar in juvenile and adult rats. Exposure levels at the NOAEL in the juvenile rats (1 mg/kg/day) were below those reached in paediatric patients.

2.5.4.5.2. Studies conducted in dogs

a) Oral studies

Table 3: summary of oral toxicity studies in juvenile dogs

Species **Study status** **Study ID / GLP**	**Route, duration, doses**	**Main findings**
Dog (Beagle) aged PND4 2/sex/group DRF study SN 07367 GLP: Yes	Oral (gavage) 14 days (PND 4-17) 0, 10, 30, 60 mg/kg/day	• 30: body weight loss and ↓body weight gain in F (1/2; up to PND13; not seen at 60 mg/kg) • 60: ↓body weight gain in M (PND 16-18)
Dog (Beagle) aged PND 4 8-11/sex/group with 3/sex/group for recovery; TK: 4-6/sex/group Pivotal study SN 07194 GLP: Yes	Oral (gavage) 9 months (PND 4-276) + 3-month recovery [TK animals: 29 days; PND 4-32] 0, 5, 15, 60 mg/kg/day	• ≥5: clinical signs (clear discharge from the eyes prior dosing and 1-2 hours post-dose), ↓**body weight** (in F: 19.3%, 20.0%, 21.8%; PND 276), hematology (↓platelet count on PND32), serum chemistry (↑ALP), **lungs** (white areas, vacuolated macrophages in subpleural and perivascular alveoli - consistent with phospholipidosis), **ileum** (vacuolated macrophages in Peyer's patch, cytoplasmic vacuolation of neurons in Auerbach's plexus), **colon** (vacuolated macrophages in Peyer's patch) • ≥15: hematology (↑platelet volume on PND32 in F), serum chemistry (↑ALAT, ↓triglycerides), urinalysis (↑volume, ↓specific gravity and osmolality), **ileum** (vacuolated macrophages in lamina propria), **colon** (cytoplasmic vacuolation of neurons in Auerbach's plexus) • 60: clinical signs (pale gums prior dosing and 1-2 hours post-dose), ↓**body weight** (in M: 12.4%; PND 276), neurobehaviour assessment (↑ systolic, diastolic, and mean arterial pressure in M), hematology (↓mean corpuscular hemoglobin concentration on PND 109 and 270), **brain** (cytoplasmic vacuolation of neurons in geniculate nuclei of midbrain in 1F found dead on PND35) <u>End of recovery</u> • ≥5: ↓**body weight** (in F: 17.7%, 12.6%, 10.6%; PND367) • ≥15: clinical signs (clear discharge from the eyes in F), **ileum/colon** (cytoplasmic vacuolation of neurons in Auerbach's plexus in F)

Table 4: toxicokinetic parameters in the oral juvenile dog study (sexes combined)

Study	Time	Dose (mg/kg)	Cmax (ng/mL)	AUC (ng.h/mL)	Exposure multiple (AUC)* 2 to <7 years	2 to <7 years
9-month JAS, dog SN 07194	PND4	5	449	7325	0.3	0.3
		15	931	16450	0.7	0.7
		60	1895	32750	1.4	1.3
	PND32	5	1640	32250	1.4	1.3
		15	4025	76400	3.3	3.1
		60	5905	120500	5.2	4.8
	PND102	5	703	11200	0.5	0.4
		15	1665	29950	1.3	1.2
		60	2690	49800	2.2	2.0
	PND263	5	894	17550	0.8	0.7
		15	2525	52650	2.3	2.1
		60	5340	112500	4.9	4.5

* based on AUC0-24 levels of 23,000 and 25,000 ng.h/mL in children aged 2 to <7 years and 7 to 17 years, respectively, treated with posaconazole gastro-resistant powder and solvent for oral suspension (see SmPC 5.2)

The dose-range finding study in juvenile dogs (no. SN 07367) was conducted with POS oral suspension to determine doses for the definitive study. The findings were consistent with those previously observed with POS in previous nonclinical studies and there were no new POS-related toxicities identified.

The objective the definitive study was to evaluate the potential for neurotoxicity of POS when administered orally via gavage to juvenile beagle dogs for 39 weeks beginning on PND 4 and to assess the toxicokinetics of POS. A recovery period of 3 months was included. This study targeted evaluation of the nervous system in order to address the finding of neuronal phospholipidosis observed in adult dogs. Animals were dosed once daily by oral gavage from PND 4 through 276 for the toxicology subgroup and from PND 4 to PND 32 for the toxicokinetic subgroup. Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, ophthalmologic examinations, neurobehavioral assessments (motor, sensory, and autonomic pathways), clinical pathology, and gross and histopathological examinations.

There were no test article-related mortality and clinical findings mostly resolved during the recovery period; however, an increased incidence of clear discharge from the eyes was still seen in females at ≥15 mg/kg/day. Lower mean body weight gains and subsequently lower mean body weights were observed vs. controls at the end of the dosing period (PND 276) in males at 60 mg/kg/day and at all dose levels in females. These effects did not correlate with decreases in food consumption and did not persist through the recovery period for males. However, body weights remained lower than the control group throughout the recovery period for females, and these effects was considered adverse due to the percent differences from the control group (>10%).

Some clinical pathology changes were observed during the treatment period, but none persisted after the 91-day recovery period. There were no POS-related ophthalmologic findings. POS-related increases in blood pressure were observed in the 60 mg/kg/day-dosed males on PND 108 and 269. No neurobehavioral findings were observed at any POS dose level.

Posaconazole-related microscopic findings were all considered non-adverse and were limited to vacuolation of macrophages consistent with phospholipidosis (observed in previous studies in adult animals) in the following tissues: the lamina propria in the ileum in the 15 mg/kg/day males and 60 mg/kg/day dose males and females; the subpleural and perivascular alveoli of the lung at all doses; the neuronal bodies of the Auerbach's plexuses in the ileum in males at all doses and in the colon in males at 15 and 60 mg/kg/day; the Auerbach's plexuses in the ileum and colon in females at 15 and 60 mg/kg/day; in the Peyer's patches of the ileum and colon in all POS-treated dose groups; and in the neurons of the geniculate nuclei in the midbrain of one dog that died on PND 35. The neuronal vacuolation in the midbrain was similar to that observed in the Auerbach's plexuses in dogs examined

from the primary necropsy but was not observed in any other dog. This neuronal vacuolation is likely test article-related but did not contribute to the death of this dog.

After the 3-month recovery period, the only POS-related finding that persisted was cytoplasmic vacuolation of the neurons in the Auerbach's plexus of both the colon and ileum in the 15 and 60 mg/kg/day group females. The lower number of vacuolated neurons and less extensive vacuolation than noted at the primary necropsy indicated that recovery was ongoing.

b) Intravenous studies

Table 5: summary of intravenous toxicity studies in juvenile and young adult dogs

Species **Study status** **Study ID / GLP**	**Route, duration, doses**	**Main findings**
Dog (Beagle) aged PND 14– main 4/sex/group + recovery 4/sex/group Pivotal study TT# 12-9018 GLP: Yes	Intravenous (bolus) 6 weeks (PND 14-56) + 5-month recovery 0 (vehicle)[a], 0 (placebo)[b], 10 mg/kg/day	Clinical observations (thinness, prominent backbone, partly closed eyes, labored breathing, fur staining, liquid and/or foamy material), ↓**body weight gain** from PND31/38 (26-35% PND 14-56), opthalmology (↑incidence of serous ocular discharge), serum chemistry (↑ALAT, ASAT, ALP, globulin; ↓creatinine, total protein, albumin, A:G ratio, calcium), **brain** (neuronal vacuolation, dilation of lateral ventricles in 3/4 M and 2/4F), **adrenal glands** (↑wt, hyperplasia of the zona fasciculata, atrophy of the zona glomerulosa), **thyroid gland** (↑wt in F, ↑amount of colloid), **spinal cord/ small intestine/ large intestine/ urinary bladder** (neuronal vacuolation), **lung** (macrophage accumulation in alveoli), **spleen/ lymph nodes/ Peyer's patch/ thymus** (histiocytic vacuolation) <u>End of recovery</u> <u>↓**body weight gain** (5-22% PND 56-96)</u>
Dog (Beagle) aged 10 weeks– main 5/sex/group + recovery 4/sex/group Pivotal study TT #14-1001 GLP: Yes	Intravenous (bolus) 13 weeks + 9-week recovery 0, 10 mg/kg/day	**Mortality** (1F on Day 25 with clinical signs, clinical pathology findings, and postmortem changes consistent with hemorrhage related to physical trauma; role of test-article as a contributing cause for the hemorrhage could not be ruled out)
Dog (Beagle) aged 31-35 weeks ("young adult")– 4/sex/group Pivotal study TT #13-1062 GLP:	Intravenous (15-min infusion) 3 months 0, 9 mg/kg/day	**Lung** (pale foci in 7/8; likely related to phospholipidosis)

[a] vehicle = 5% dextrose for injection; [b] placebo = Sulfobutylether-β-cyclodextrin, EDTA and water

Table 6: toxicokinetic parameters in the intravenous juvenile dog studies (sexes combined)

Study	**Time**	**Dose (mg/kg)**	**Cmax (ng/mL)**	**AUC (ng.h/mL)**	**Exposure multiple (AUC)***	
					2 to <7 years	**2 to <7 years**
6-week JAS, dog TT#12-9018	PND50	10	9881	186413	6.0	4.2
13-week JAS, dog TT#14-1001	Study week 7 (≈PNW17)	10	8210	138500	4.5	3.1
3-month tox, dog TT#13-1062	Study Day 1 Study Week 7	9 9	4890 10850	49500 153000	1.6 4.9	1.1 3.5

*taking into consideration AUC0-24 levels of 31,100 and 44,200 ng.h/mL in children aged 2 to <7 years and 7 to 17 years, respectively (see SmPC 5.2)

- **Study TT#12-9018: An Age-Targeted 6-Week Intravenous Injection Toxicity Study of POS with a Five-Month Postdose Period in Juvenile Beagle Dogs**

The objective of this study was to determine the potential toxicity of POS IV Solution when given by daily intravenous injection to juvenile beagle dogs for 6 weeks beginning on PND 14, with an evaluation of reversibility following a 5-month recovery period. Assessment of toxicity was based on clinical signs, body weights, food consumption, ophthalmology, observation battery and neurological examination, clinical pathology parameters (hematology, coagulation, and clinical chemistry), gross necropsy findings, organ weights, and histopathological examinations.

POS related clinical sings included fur staining (on limbs and/or abdomen) and liquid and/or foamy material. In addition, thinness and prominent backbone were observed in 2 males; one of these males also exhibited labored breathing and the other had partially closed eyes. At Week 6 ophthalmologic examinations, there was a slight increase in incidence of serous ocular discharge. This was considered as a minor non-adverse finding, shown to be reversible. Compared to vehicle controls, POS-related reductions in body weight gains were observed beginning on PND 31 in males and on PND 38 in females that persisted until the end of the recovery period. Slight and reversible, POS-related clinical chemistry changes were also noted at Week 7 postpartum.

At the end of the dosing period, POS-related histological changes included dilation of the lateral ventricles of the brain and findings consistent with phospholipidosis (neuronal vacuolation) in the brain, spinal cord, myenteric and/or submucosal plexi, small intestine, large intestine and urinary bladder; accumulation of alveolar macrophages in the lungs; and histiocytic vacuolation in the spleen, lymph node, Peyer's patches and thymus. Additional histological findings attributable POS were observed in the adrenal glands (hyperplasia of the zona fasciculata and atrophy of the zona glomerulosa) and thyroid (increased amount of colloid). At the end of the recovery period, there were no POS-related gross, microscopic or organ weight findings, indicating recovery of all findings.

In conclusion, daily intravenous administration of posaconzole at 10 mg/kg/day to juvenile beagle dogs from PND 14 to 56 resulted in adverse clinical signs at the end of the treatment phase and a reduction in body weight and/or body weight gain. Reversible changes in some serum chemistry parameters were noted. At the end of the treatment phase, POS-related histomorphologic changes were present in the brain, spinal cord, adrenal glands, thyroid gland, urinary bladder, lung, spleen, lymph node, small intestine, Peyer's patches, large intestine and thymus; however, these changes were reversible by the end of the recovery period. Based on these findings a NOAEL was not established.

- **Study TT#14-1001: Three-Month Intravenous Toxicity Study in PostWeaning Juvenile Dogs with a 9-Week Treatment-Free Period**

The purpose of this study was to determine the potential effects on brain and ventricle size of POS when administered intravenously at 0 or 10 mg/kg/day to juvenile dogs (approximately 10 weeks old at study start) once daily for approximately 3 months. The first 5 animals/ sex/group were designated for interim necropsy at the end of treatment phase, and the last 4 animals/sex/group were designated for final necropsy after a 9-week treatment-free period. Assessment of toxicity was based on mortality, clinical observations, body weights, clinical pathology evaluations (one early-death animal only) and anatomic pathology evaluations. Drug concentrations in the plasma of treated and control animals were determined. In addition, exploratory measurement of drug concentrations in the CSF and brain samples from all groups were conducted. Exploratory MRI examinations were conducted on the brain to evaluate the brain ventricle volumes.

A drug-treated female dog was sacrificed on Day 25, with clinical signs, clinical pathology findings, and postmortem changes consistent with hemorrhage secondary to physical injury. However, the role of the test article as a contributing cause for the hemorrhage could not be ruled out. Additional changes

in this dog included vacuolated macrophages in some lymphoid tissues (lymph node and Peyer's patches), consistent with phospholipidosis, and changes secondary to hemorrhage and stress.

There were no test article-related clinical observations or body weight changes. There were no test article-related brain weight changes or gross findings following 13 weeks of dosing or the 9-week treatment free-period. There were no test article-related histomorphologic findings in the brain following 13 weeks of dosing.

There were no test article-related effects on brain ventricle volumes in the exploratory MRI examinations. In addition, POS mean concentrations in CSF and brain (exploratory) are presented in **Table *7***.

Table 7: Summary Mean CSF and Brain POS Concentration in Dogs Following 3-Month Dosing of POS (TT #14-1001): Week 14

Week	Dose (mg/kg/day)	Sex	CSF (ng/mL)	Brain (ng/mL)
14	10	Female	2.93	1079.8
		Male	2.31	1347.4

- **Study TT#13-062: Three-Month Intravenous Infusion Toxicity Study in Dogs**

The purpose of this study was to evaluate the potential toxicity (with a targeted evaluation of the brain) of POS administered intravenously for approximately 3 months at 0 or 9 mg/kg/day (4/sex/group) to young adult dogs (31 to 35 weeks of age at study start). Assessment of toxicity was based on mortality, clinical observations, body weights, food consumption, gross examination, organ weight of brain, and thorough histomorphologic examination of brain. Drug concentrations in the plasma in the treated and control samples were determined. In addition, exploratory measurement of drug concentration in the CSF, and brain samples from all groups were conducted. Exploratory MRI examinations were conducted on the brain to evaluate the brain ventricle volumes.

All animals survived to scheduled sacrifice. There were no test article-related clinical signs. There were no test article-related body weight or food consumption changes.

There were no test article-related changes in brain weights or histomorphologic 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 multiple pale foci on the lungs of 7 of the 8 dogs treated with POS which were considered likely due to phospholipidosis.

There were no test article-related changes in brain ventricle volumes as determined by MRI. No differences in brain ventricle volume were seen between groups. POS concentrations in CSF and brain are presented in Table 8.

Table 8: Summary Mean CSF and Brain POS Concentration in Dogs Following Intravenous Administration of POS (TT #13-1062): Study Week 14

Week	Dose (mg/kg/day)	Sex	CSF (ng/mL)	Brain (ng/mL)
14	10	Female	4.10	1359.61
		Male	7.43	2442.29

c) Discussion and conclusion on juvenile dog studies

The definitive juvenile dog study (SN 07194) conducted orally targeted evaluation of the nervous system in order to address the finding of neuronal phospholipidosis observed in adult dogs. The results were consistent with those previously observed with posaconazole and there were no new posaconazole-related toxicities. Neuronal phospholipidosis was observed in the midbrain (1 female at

60 mg/kg/day) and Auerbach's plexus (males at all doses, females at ≥15 mg/kg/day); as with the neuronal phospholipidosis observed in the adult dogs, there were no effects on motor, sensory and autonomic pathways at all doses. The NOAEL was 15 mg/kg/day for males and ≤ 5 mg/kg/day for females based on decreased body weights (males at 60 mg/kg/day, females at ≥ 5 mg/kg/day) and vacuolation of macrophages in the ileum, colon, and/or Peyer's patches at ≥ 15 mg/kg/day and the lungs at all dose levels consistent with phospholipidosis. After the 3-month recovery period, the only POS-related finding that persisted was cytoplasmic vacuolation of the neurons in the Auerbach's plexus of both the colon and ileum in the 15 and 60 mg/kg/day group females. The lower number of vacuolated neurons and less extensive vacuolation than noted at the primary necropsy indicated that recovery was on-going.

Two studies were then conducted with daily administration of the POS IV solution to juvenile beagle dogs at a dose of 10 mg/kg/day for 6 weeks to preweaning juvenile dogs (study TT#12-9018), and for 13 weeks to post-weaning juvenile dogs (study TT#14-1001).

- ✓ In study TT#12-9018, dogs were treated from PND 14 to 56. The age of animals during the treatment period generally corresponds approximately to a human developmental age from 3 months to 2 years of age (Beck et al., 2006). The results from this study were consistent with the known effects of POS and/or azole antifungals with the exception of enlargement (dilatation) of the lateral ventricles of the brain. This finding was noted in 2/4 females and 3/4 males at the end of the dosing phase and was most likely attributed to POS IV solution, since it was not observed in either the vehicle or placebo control groups. There were no neurologic or behavioral abnormalities in the juvenile dogs with enlarged ventricles, no histomorphologic changes in the surrounding brain parenchyma or in the ependymal cells of the lateral ventricles, no toxicologically relevant ophthalmic findings and, other than the expected neuronal phospholipidosis, there were no other abnormalities in the brain. Following the 5-month treatment-free period, histomorphologic dilatation of the lateral ventricles was similar in incidence between placebo control and POS IV solution-treated groups.
- ✓ Study TT#14-1001 was conducted to further assess the potential effects of POS IV solution on the brain and ventricle size using older (post-weaning) dogs treated for 13 weeks from 10 weeks of age. The age of the juvenile dogs during the treatment period corresponds approximately to a human developmental age from 2 to 17 years of age (Beck et al., 2006). Ventricular development was evaluated in the brain during dosing by MRI following 4, 8 and 12 weeks of POS IV solution administration. The results showed that the lateral, third and fourth ventricles were no different from controls, as determined by MRI examination and confirmed by macroscopic and microscopic evaluation of the brain.

Moreover, a 3-month study (TT#13-602) with targeted evaluation of the brain was conducted in young adult dogs (31 to 35 weeks of age at study start) dosed intravenously once daily at 9 mg/kg to evaluate the finding of ventricular dilatation. Results indicated that there were no test article-related changes in brain ventricle volumes as assessed by MRI evaluations following 3, 7 and 12/13 weeks of POS IV solution administration. The lack of enlarged ventricles was confirmed at necropsy. The ventricles of the brain in treated dogs were similar to control dogs when evaluated by gross observation and there were no histomorphologic brain findings.

The results of these studies were consistent with the known effects of POS and/or azole antifungals with the exception of enlargement (dilatation) of the lateral ventricles of the brain observed only when POS IV solution was administered to juvenile dogs aged 2 to 8 weeks, which corresponds to human development from age 3 months to 2 years (Beck et al., 2006).

It is important to note that development of the ventricles in the brain is markedly different between dogs and humans. In dogs, there is a period of rapid expansion of the ventricles relative to brain size from 3 to 10 weeks postnatal, whereas in humans this period of rapid ventricular expansion occurs in

utero (Kii et al., 1998; Knickmeyer et al., 2008; Roza et al., 2008). Thus, the developmental stage of ventricular growth differs markedly between dogs and humans, which makes it complex to translate the POS IV solution-related findings in very young juvenile Beagle dogs to humans. Brain ventricular enlargement was not observed during or after POS IV solution administration to post-weaning juvenile dogs aged 10 to 22 weeks, representing human development from 2 to 17 years of age. This finding was also not observed following POS IV solution administration to young adult dogs for 3 months or young adult monkeys for 1 month (study no. SN 08110, refer to POS IV solution Marketing Application), representing human development from 17 years through adulthood. Plasma concentrations observed in these studies exceeded those at which brain ventricular enlargement was observed. Therefore, the potential risk of enlarged ventricles is not considered relevant to adults (≥ 18 years) or to children aged ≥ 2 to 17 years.

In conclusion, the MAH believed that existing nonclinical study data as well as available human clinical study data (both adult and paediatric), support the safe administration of POS IV solution and POS PFS in paediatric patients ≥2 years of age.

The CHMP noted that the findings of the 9-month oral juvenile dog study initiated in neonatal animals (4 days of age) were in line with those observed in adult dogs. Neuronal phospholipidosis was reported in the Auerbach's plexus of both the colon and ileum at the end of treatment period, with recovery still ongoing after a 3-month recovery period in females dosed at 15 mg/kg/day and above. Neuronal vacuolation was also noted in the geniculate nuclei of the midbrain of one high dosed female dead prematurely. To further address this point, further sections of midbrain were obtained to fully evaluate the geniculate nuclei (medial and/or lateral) in the remaining dogs (when possible). Vacuolation of neurons in these sections or in any other section of brain were not observed in other animals. These findings were not associated with functional effects on motor, sensory and autonomic pathways at up to 60 mg/kg/day (x2.5-3.6 clinical exposure), as in adult animals where neuronal phospholipidosis seen in dogs was considered as unlikely to be of clinical significance. Of potential relevance for paediatric development is the decrease in body weight values seen in high dosed males and all treated females, shown to be non-reversible in females at all dose levels. At the NOAEL identified for males, exposure levels were either lower or slightly above the clinical exposure (x0.7-3.3) while there was no NOAEL for females. This study was reviewed previously by the CHMP, and constitutes the basis of the wording for SmPC section 5.3.

Studies conducted by the intravenous route no. TT#12-9018 and TT#13-602 were discussed previously by the CHMP during the line extension procedure for approval of the intravenous formulation (EMEA/H/C/000610/X/33/G). At that time, the MAH did not apply for any paediatric indication and the following conclusions were made: "*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 MAH 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 SPC and the use of posaconazole in patients under 18 years of age is not recommended.*"

Since then, a 13-week study performed in dogs aged 10 weeks at treatment initiation and treated at the same dose level (10 mg/kg/day) was completed. Enlargement of lateral ventricles in the brain was not reported by MRI examination during the study and at necropsy by macroscopic and microscopic evaluation of the brain. This would confirm that in dogs, posaconazole-induced enlargement of brain ventricle occurs after exposure during the earlier stages of postnatal brain development (from PND14) but not at later stages (from 10 weeks of age, or in young adults). It is noted that this finding was not observed in the oral juvenile dog study initiated in 4 days old animals (as described in SmPC 5.3).

The MAH discussed the translation to human infants of posaconazole-related enlargement of brain ventricle volume noted in the juvenile dog study #TT-12-9018 based on an interspecies comparison of brain ventricle development. In essence, it is suggested that this effect may not be relevant to children above 2 years of age since it occurs during a period of rapid ventricular extension which takes place from 3 to 10 weeks postnatal in dogs vs. prenatally (*in utero*) in humans. From the provided literature, it appears the onset of ventricular extension ranged from PND 23-32 in 14 dogs, this phenomenon progressing rapidly up to PND75 followed by a slower increase up to PND210 (Kii et al., 1998). In humans, both decreases and increases in ventricular size have been reported *in utero* (Roza et al., 2008), with reports of a rapid increase of lateral ventricle volume by the first week of life (due to an increase in volume of CSF due to change from low fetal to high neonatal pressure circulatory state) followed by gradual increases during the following 6 months (Kii et al., 1998). Other authors report a large increase in volume of lateral ventricles during the first postnatal year followed by a decrease during the second year (Knickmeyer et al., 2008). Therefore, the CHMP considered that it would appear that the sensitive period for brain ventricle development in dogs would correspond to a developmental stage spanning the first post-natal year in humans.

2.5.5. Implications of the assessment of non-clinical data for the Safety Specification of the Risk Management Plan (RMP)

The implications summarised in the table below were considered by the CHMP to be acceptable:

Juvenile toxicity	
Enlarged ventricles in the brains of juvenile dogs, with no neurological or behavioural or developmental abnormalities were observed with POS IV solution administration from post-natal days 14-56 (human equivalent age <2 years). This finding was shown to be reversible after treatment cessation and was not observed with oral administration in juvenile rats or dogs or when POS IV was administered to juvenile dogs aged 70-154 days of age.	Uncertain relation to administration in children aged 3 months-2 years. No human relevance for adult indications and for clinical development in pediatrics of ≥ 2 years of age. Human relevance unknown for pediatrics < 2 years of age.

Section 5.3 of the SmPC states that the clinical significance of this finding is unknown; therefore, the use of posaconazole to patients under 2 years of age is not recommended.

2.5.6. Ecotoxicity/environmental risk assessment

This extension application contains new environmental data,

Updated prevalence data:

Indication		**Estimated Size of Population (N) in 2013**
Treatment	Invasive Aspergillosis	64 000 [a]
	Fusariosis	246 [b]

		[Incidence: 6/1000 for HSCT (41,000 allogenic and autologous)]
	Chromoblastomycosis and mycetoma [c]	Rare [d]
	Coccidioidomycosis [c]	Rare [d]
	Oropharyngeal candidiasise [e]	Estimated 148,000 oral candidiasis and 96,200 oesophageal candidiasis [f]
	Acute Myeloid Leukemia [8]	55,000 [a] (prevalence; 19,000 incidence)
	Myelodyspastic Syndrome [8]	25,000 a (prevalence; 8,000 incidence)
	HSCT (Allogenic) [4]	41,000 allogenic and autologous HSCTs per year (approximately 43% allogeneic)*
Total Population		429,200

a Rounded to the nearest thousand.
b This number is not included in the total because it is already included in the row below for total HSCT.
c Chromoblastomycosis, mycetoma, and coccidioidomycosis are rarely observed in Europe. These infections are usually imported to Europe from endemic regions. There are no published incidence estimates of these infections in Europe.
d Per the European Commission, rare is defined as a disease affecting fewer than 5 people in 10,000.
e The majority of patients with oropharayngeal candidiasis will be treated with and respond to topical antifungals. Patients who are immunosuppressed are more likely to require treatment with a systemic antifungal such as an azole (including possible use of posaconazole) [25] [26].
f This is based on estimated 2 million and 1.3 million global incidence of oral candidiasis and oesophageal candidiasis and prorated to EU28 2020, Norway, Iceland and Liechtenstein.

The overall table summarising study results has consequently been updated and is provided below:

Summary of main study results

Substance (INN/Invented Name): Noxafil (Posaconazole)			
CAS-number (if available): 171228-49-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow}	OPPTS 830.7560	pH 7 = 4.15	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	pH 5 = 4.06 pH 7 = 4.15 pH 9 = 4.10	not B
	BCF	29-36 L/kg (fish)	not B
Persistence	DT50	Transformation Products in sediment (20°C): >180 d	vP
Toxicity	NOEC	0.041 mg/l (algae)	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (prevalence data) Fpen = 0.0829%	0.33	µg/L	> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Soil: Log Koc = 5.12 to 5.52 Kd = 1875 to 5820 Sludge: Log Koc = 3.6	

		Kd = 1607			
Ready Biodegradability Test	OECD 301	0% (28d), not readily biodegradable k_{STP} (0 h-1)			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 0.5-4.5d $DT_{50, sediment}$ = 8.7-11.9d $DT_{50, whole\ system}$ =0.7-13.3d % shifting to sediment = 29.3 (day 28)			$DT_{50\ sediment}$ Transformation products: M1: stable M2: 215.9 d M3: 358.1 d
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	33	µg/L	*Pseudo-kirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	244	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	206	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	10^6	µg/L	Sewage slude mixed population
Phase IIb					
Calculation	**Value**	**Unit**			**Remarks**
PEC $_{surfacewater}$, refined	0.073	µg/L			Fpen = 0.0829% Koc soil (geomean) = 182602.16
PEC $_{sediment}$	230	µg/kgdwt			Kd soil (geomean) = 3151
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	29-36	L/kg	*Lepomis macrochirus*
Sediment dwelling organism	OECD 218	NOEC	76	mg/kg	*Chironomus riparius*

2.5.7. Discussion and conclusions on non-clinical aspects

To support the extension of indication of NOXAFIL intravenous solution to patients from 2 to 18 years of age, and approval of a new oral formulation for use in the same patient population, the MAH submitted a series of juvenile toxicity studies conducted in rats and dogs by the oral route of administration, as well as studies wherein juvenile and young adult dogs were treated intravenously.

In the pivotal 12-week rat and 9-month dog juvenile toxicity studies, treatment was initiated in animals of an age generally covering the paediatric population from birth (i.e. 7 days old rats and 4 days old dogs). In these studies, the toxicological profile of posaconazole was consistent with that already defined in adult animals of each species. There was no additional target organ, or no new toxic effect of concern identified in any study. In particular, there was no treatment-related impact on the reproductive capacity of rats, and no effect on neurobehavioral parameters evaluated in both species. The latter aspect is of particular importance in dogs since neuronal phospholipidosis was reported in line with adult dog studies where it was considered as unlikely to be of clinical significance. A treatment-related effect on body weight was observed in juvenile dogs and was not reversed at all dose levels in females. NOAELs of 1 mg/kg/day and 15 mg/kg/day were determined in rats and in male dogs, respectively, whereas none could be determined in female dogs. Considering the toxicokinetic data in each study, it has to be considered that there was no safety margin in rats and

female dogs, while the exposure levels at the male dog NOAEL was either lower or slightly above the clinical exposure (x0.7-3.3).

A 6-week juvenile toxicity study was conducted in dogs with the intravenous solution at a dose of 10 mg/kg/day and evaluated previously by the CHMP. At that time, it was concluded that in addition to the well-characterised POS toxicities, enlargement of the lateral ventricles in the brain was observed in this study. There were no neurological or behavioural abnormalities in the dogs with this finding. It was pointed out that 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, brain ventricular dilation was not reported in young adult rats and young adult monkeys dosed intravenously for three months with a suspension formulation of not further developed for clinical application at systemic exposures similar or exceeded those achieved in the juvenile dog study testing POS IV solution. The MAH 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 was considered as unknown, although the fact that the finding was reported in only one study provides reassurance. This finding was included in section 5.3 of the SmPC with a statement that the use of posaconazole in patients under 18 years of age is not recommended.

In the application covered by this Assessment Report, an additional 13-week study conducted in juvenile dogs with the POS IV solution at the same dose level of 10 mg/kg/day is submitted. Animals were 10 weeks of age at initiation. Brain ventricular dilation was not reported by MRI examination during the study and at necropsy by macroscopic and microscopic evaluation of the brain. This would confirm that in dogs, posaconazole-induced enlargement of brain ventricle occurs after exposure during the earlier stages of postnatal brain development (from PND14) but not at later stages (from 10 weeks of age, or in young adults). It was noted that this finding was not observed in the oral juvenile dog study initiated in 4 days old animals, however lower systemic exposure levels were reached in that study. Section 5.3 of the SmPC now specifies that the use of posaconazole in patients under 2 years of age is not recommended.

Assessment of paediatric data on non-clinical aspects

The MAH discussed the translation to human infants of posaconazole-related enlargement of brain ventricle volume noted in the juvenile dog study initiated in 14 days old dogs based on an interspecies comparison of brain ventricle development. Further information was requested on this issue since 10 week-old dog (not shown to develop the lesion) would correspond to children older than 2 years of age based on an overall developmental interspecies comparison (Buelke Sam 2003). The MAH explained that human risk assessment should rely primarily on specific organ system development. Since some literature data would suggest that the sensitive period for brain ventricle development in dogs would correspond to a developmental stage not exceeding the first post-natal year in humans, this position was viewed as acceptable. As the extension of indication is sought for patients from 2 years of age wherein no adverse effects indicative of morphological changes in the brain were reported, SmPC Section 5.3 now indicates that the clinical significance of this finding is unknown and that the use of posaconazole in children below 2 years of age is not recommended. It was also recommended that a common wording for juvenile toxicity findings should be included in SmPC 5.3 of any pharmaceutical formulation indicated in paediatric patients for consistency of the information provided to the prescriber. Therefore, a slight amendment of the SmPC Section 5.3 wording for Noxafil 300 mg concentrate for solution for infusion was carried out.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

- **Tabular overview of clinical studies**

Study Number (Status) [CTD Location] Number of Study Sites (Regions)	Design (Indication)	Number of Participants by Intervention Group	Study Population (N)	Primary Endpoint(s)
Study of IV and PFS Formulations				
5592-097 Completed [Ref. 5.3.3.2: P097MK5592] 29 sites (11 countries)	Nonrandomized, multicenter, open-label, sequential dose-escalation study of the safety, tolerability, and PK of the POS IV solution and POS powder for suspension (PFS) in immunocompromised children and adolescents (2 to <18 years) with neutropenia or expected neutropenia Duration: approximately 36 months	For all dose cohorts, the maximum total treatment duration was 28 days. **Dose Cohort 1** Day 1: POS 3.5 mg/kg IV BID Days 2-10: POS 3.5 mg/kg IV QD Days 11-20: switch to POS PFS 3.5 mg/kg PO QD or continue POS 3.5 mg/kg IV QD Age Group 1 *(2 to <7 years):* 14 subjects treated Age Group 2 *(7 to <18 years):* 21 subjects treated **Dose Cohort 2** Day 1: POS 4.5 mg/kg IV BID Days 2-10: POS 4.5 mg/kg IV QD Days 11-20: switch to POS PFS 4.5 mg/kg PO QD or continue POS 4.5 mg/kg IV QD Age Group 1: 15 subjects treated	115 treated subjects: 67 males (58.3%) 48 females (41.7%) Median age 8.0 years (range, 2-17 years) Median weight 28.6 kg (range, 10.2-101.6 kg)	**Primary Endpoints** **PK Endpoints:** Plasma pharmacokinetics profile [AUC, Cmax, Cmin, and Cavg] following administration of POS IV solution and POS PFS **Secondary Endpoints** **Safety Endpoints:** Adverse events, hematology and blood chemistry, vital signs, electrocardiogram results. **Efficacy Endpoints:** There are no efficacy endpoints for this study.

Study Number (Status) [CTD Location] Number of Study Sites (Regions)	Design (Indication)	Number of Participants by Intervention Group	Study Population (N)	Primary Endpoint(s)
		POS OS 18 mg/kg/day PO, divided into 3 doses (TID) Age Group 1: 15 subjects treated Age Group 2: 30 subjects treated **POS OS 12 mg/kg/day PO, divided TID** Age Group 3 (*3 months to <2 years*): 1 subject treated		
Abbreviations: AUC = area under the concentration-time curve; BID = twice a day; Cavg = average steady-state plasma concentration; Cmax /Cmin = maximum / minimum observed plasma concentration; IV = intravenous; OS = oral suspension; PFS = powder for oral suspension; PK = pharmacokinetic(s); PO = *per os* (by mouth); POS = posaconazole; QD = once a day; Tmax = time to maximum observed plasma concentration; TID = 3 times a day.				

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

2.6.2.1. Introduction

Posaconazole (POS, MK-5992, NOXAFIL ®) is a broad spectrum systemic triazole antifungal that inhibits lanosterol 14 α-demethylase (also known as CYP51), an enzyme essential for the biosynthesis of ergosterol comprising the cell membrane microorganisms.

The currently marketed formulations of POS are an OS (oral suspension), an IV and an oral delayed-release tablet (also as referred to as a gastro-resistant tablet, hereafter referred as tablet). The POS tablet was developed to overcome some of the absorption limitations encountered with the OS formulation including the need of BID or TID dosing administered with a meal or nutritional supplement in order to achieve target pharmacokinetic (PK) exposures. The POS IV formulation was developed to fulfil an unmet medical need for patients who are unable to take or absorb an oral formulation.

POS is currently approved in many countries and regions including US and EU for prophylaxis and, in some countries, for salvage treatment of antifungal infections in adults. Specifically approved indications include the use as treatment of refractory IFI, prophylaxis of IFI in patients at high risk of developing these infections, and as treatment of oropharyngeal candidiasis (OS only).

The POS tablet is supplied at a dosage strength of 100 mg and the IV formulation as a solution containing 300 mg POS per 16.7 mL solution (18 mg/mL).

The recommended dosing regimen for IV and tablet in adults is 300 mg BID on the first day, as a loading dose followed by 300 mg QD as a maintenance dose.

The key PK properties obtained from adults' data are briefly summarized below:

- POS tablets are absorbed with a median Tmax of 4 to 5 hours and exhibit dose proportional PK after single and multiple dosing up to 300 mg. F is 54%.
- POS has a distribution volume of 261 L, indicating extravascular distribution and is highly protein bound (> 98%).
- POS primarily circulates as the parent compound in plasma and does not have any major circulating metabolites. Of the circulating metabolites, the majority are glucuronide conjugates of POS with only minor amounts of oxidative (CYP40 mediated) metabolites. POS is primarily metabolized via UDP glucuronidation and is a substrate of P-gp efflux.
- POS after administration of 300 mg POS IV is slowly eliminated with a mean half-life of 27 hours and CL of 7.3 L/h. Following tablet administration, POS is eliminated with mean half-life of 26 to 31 hours and CL of 7.5 to 11 L/h. Steady-state is reached by Day 6 for both formulations.

According to these past approvals, a wealth of PK information of POS in adults is available. Hence PK properties are considered as well known in adults. Consequently, this assessment report will focus on specific and relevant PK (and PD aspects) in association with the current submission: extension of the indications of POS in children and adolescent patients from 2 to < 18 years.

As part of the paediatric investigations, an additional paediatric formulation, PFS, also referred to as powder for delayed release oral suspension has been developed. A relative bioavailability study in healthy adult volunteers was performed to investigate performance of this new formulation against the tablet formulation in clinical study P106.

PFS was supplied in sachets co-packaged with notch-tip oral dosing syringes, PIBA, suspending vehicle and mixing cups. Prior to dosing, the PFS is dispersed in suspending vehicle to obtain a 10 mL of suspension with a concentration of 30 mg/mL. A 10 mL syringe can only deliver a maximum 8 mL, therefore the POS PFS kit can deliver a maximum dose of 240 mg.

Both IV and PFS formulations were used in a Phase 1 b paediatric clinical study (P097), in support of expanding the POS indications using a PK and safety bridging strategy.

Previously, the proposed PK bridging strategy, designed in consultation with FDA and EMA, have been already used to support extrapolation of the indications supported by OS to tablet and IV formulation in adults wherein efficacy was not a primary objective. The predefined exposure target was set at ≥ 90% of subjects achieving Cavg ≥ 500 ng/mL.

Following the same PK bridging strategy (same PK exposure target) and a developed Population PK analysis (PPK), the dosing regimen initially proposed for IV and PFS in paediatric subjects aged 2 to < 18 years is a weight-based according to:

- For all paediatric patients, the proposed dose should be taken BID the first day and QD thereafter
- IV route: 6 mg/kg (maximum dose of 300 mg)
- Oral route and BW ≤ 40 kg: 6 mg/kg PFS
- Oral route and BW > 40 kg: 300 mg tablet

2.6.2.2. Methods

- Analytical methods

A HPLC/MS/MS assay procedure was used to quantify POS plasma concentration and was validated by PPD® (Middleton, WI and Richmond, VA). The plasma assay isolated POS and its internal standard from plasma using solid phase extraction followed by liquid chromatographic separations. This assay was used to support the clinical studies P097 and P106, and is presented in Table 9.

Table 9: Summary of the method of determination of POS in plasma

Method Description	PPD Method P1329.00
Analyte	SCH 56592 (Synonymous with posaconazole and MK-5592)
Internal Standard	Posaconazole-d_4 (Synonymous with SCH 56592-d_4)
Method Validation Report	PPD Validation Report, Project LPW2/AIAV, Validation of a Liquid Chromatographic-Tandem Mass Spectrometric Method for the Determination of SCH 56592 Concentrations in Human Plasma
Reference Standards	SCH 56592 (Synonymous with posaconazole and MK-5592), Lot Number L-003669433-000M023 Posaconazole-d_4, Lot Numbers 1-MRS-41-2 and 6-JUZ-55-2
Matrix	Human Plasma
Anticoagulant	EDTA
Method of Detection	LC-MS/MS
Sample Aliquot Volume	50.0 µL
Calibration Range	5.00 to 5000 ng/mL
Quality Control (QC) Concentrations	15.0, 40.0, 150, 600, and 3750 ng/mL
Highest Dilution QC Concentration	25000 ng/mL
Regression, Weighting	Quadratic, $1/conc.^2$
Demonstrated Storage Stability	149 days at -20 °C in K_3EDTA 932 days at -20 °C in K_2EDTA
Maximum Sample Storage Duration From Collection to Analysis	219 days at -20 °C
Analysis Start Date	08-JAN-2016
Analysis Completion Date	19-JUL-2018

- Pharmacokinetic data analysis

Standard non-compartmental (model independent) pharmacokinetic methods were used to calculate PK parameters. Concentration below the LLOQ observed before Tlast was set to 0 prior to the PK analysis. Estimated PK parameters were Cmax, Tmax (both observed), AUC0-24, AUC0-72, C0, Cmin, Cavg, CL and CL/F using Phoenix® WinNonlin® v.6.4 software (Certara™, Princeton, NJ).

POS PK data following both IV and PFS formulation in the paediatric population were pooled to develop a PPK model using NONMEM, version 7.2 (Globomax, 7250 Parkway Drive, Suite 430, Hanover, MD 21076 USA). The applied estimation method was FOCE with an additive model for RUV on log-transformed data.

The CHMP considered that, generally, based on the validation report, the used bioanalytical method developed for the quantification of POS, in human plasma comply with acceptance criteria regarding selectivity, sensitivity accuracy and precision. Analytical validation report was provided with satisfactory results.

Short and long-term stability of the analyte in biological matrix were tested and shown to be satisfactory. ISR were performed with satisfactory results (more than 99% of the studied sample) for all analytes.

NCA PK parameters calculation is well explained and justified. Software for Population PK analysis is considered acceptable.

2.6.2.3. Absorption

Relative bioavailability / Bioequivalence

Study P106

Design

This was a randomized, open-label, 3 period, single-dose, crossover study in healthy adult male and female subjects. This study was designed to estimate the relative bioavailability of POS PFS compared to the approved POS tablet following single-dose administration of POS under fasting conditions. The effect of food on POS PK administered as the PFS formulation was also evaluated.

13 subjects received the following three treatments in a randomized crossover design, with a minimum of 10-day washout between each treatment:

- Treatment A: 100 mg POS PFS (with water as diluent) fasted overnight for at least 10 hours
- Treatment B: 100 mg POS PFS (with water as diluent) following a standardized high-fat meal within 30 min prior to dosing
- Treatment C: 100 mg POS tablet, fasted overnight for at least 10 hours

POS product

PK sampling

Blood samples were obtained following each treatment and POS in plasma was quantified at predose, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72 hours post dose. In addition, dry blood spots (DBS) for determination of whole blood POS were also performed.

PK results

A statistical summary and comparison of POS plasma PK for each of the 3 treatments is displayed in Table 10. Arithmetic mean POS plasma concentration-time profiles in healthy adult subjects are illustrated in Figure 1 below.

The GMR (90% CI) for POS Cmax and AUC0-72 between the PFS formulation (Treatment A) and the tablet formulation (Treatment C) under fasting conditions were 1.17 (1.04, 1.33) and 1.19 (1.10, 1.28), respectively. The results indicate that under fasting conditions the POS PFS formulation achieved approximately 20% higher exposure (in terms of Cmax and AUC0-72) as compared to the tablet formulation. Median Tmax was similar for both treatments.

The GMR (90% CI) of POS Cmax and AUC0-72 between fed and fasted conditions for the PFS formulation were 0.67 (0.59, 0.77) and 0.94 (0.87, 1.02). Consumption of a high-fat meal together with the POS PFS formulation had no significant effect on AUC0-72 and resulted in a moderate (23% to 41%) decrease in Cmax.

Table 10: Statistical comparison of POS plasma PK following administration of POS PFS under fasting conditions (A), fed conditions (B) or POS tablet under fast conditions (C)

Formulation	N	GM (95% CI)			
		Cmax[a] (ng/mL)	AUC0-24[a] (hr·ng/mL)	AUC0-72[a] (hr·ng/mL)	Tmax[b] (hr)
Treatment A	13	371 (312, 441)	5058 (4257, 6010)	9957 (8160, 12149)	4.00 (3.00, 12.00)
Treatment B	13	251 (211, 298)	3933 (3310, 4673)	9367 (7677, 11431)	8.00 (6.00, 24.00)
Treatment C	13	316 (266, 376)	4414 (3715, 5243)	8389 (6874, 10237)	5.00 (4.00, 6.00)

Comparison	GMR [90% CI]		
	Cmax[c]	AUC0-24[c]	AUC0-72[c]
Treatment A vs Treatment C	1.17 [1.04, 1.33]	1.15 [1.04, 1.26]	1.19 [1.10, 1.28]
Treatment B vs Treatment A	0.67 [0.59, 0.77]	0.78 [0.70, 0.86]	0.94 [0.87, 1.02]

AUC0-24=area under the curve, 0-24 hours; AUC0-72=area under the curve, 0-72 hours; CI=confidence interval; Cmax=maximum concentration; GM=Geometric least-squares mean; GMR=geometric mean ratio; PFS=powder for oral suspension

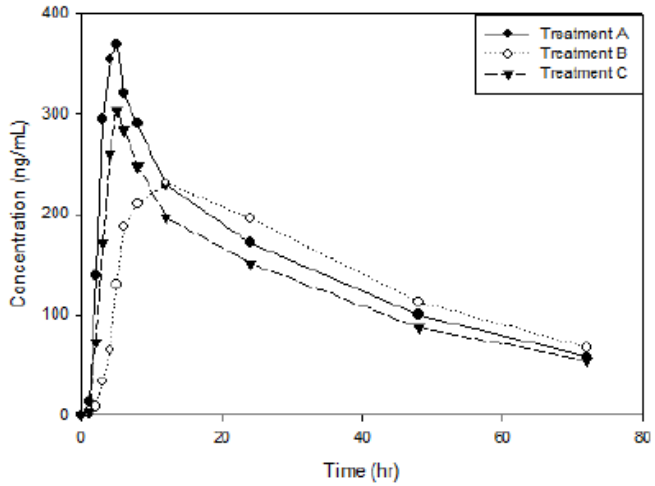
Treatment A: Single dose, oral administration of 100-mg posaconazole as a PFS under fasting conditions
Treatment B: Single dose, oral administration of 100-mg posaconazole as a PFS after consumption of a high-fat meal
Treatment C: Single dose, oral administration of 100-mg posaconazole as 1 tablet under fasting conditions

[a] Back-transformed least squares mean and confidence interval from mixed effects model performed on natural log-transformed values

[b] Median (Minimum, Maximum)

[c] GMR = Geometric least-squares mean ratio between treatments

Linear Scale



Semilogarithmic Scale

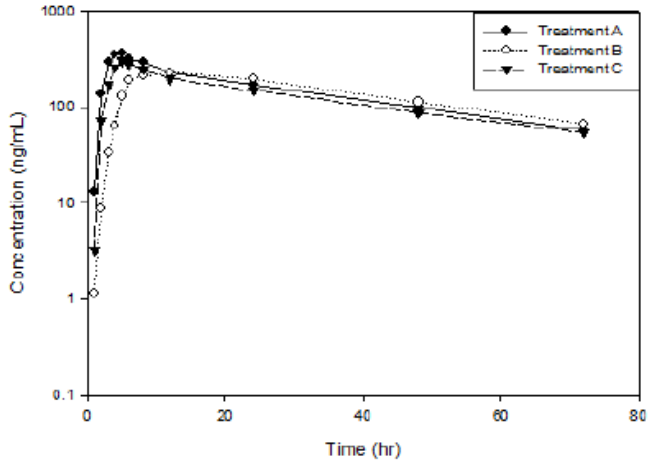


Figure 1: Arithmetic mean POS plasma concentration following the three treatments

The CHMP noted that a dedicated clinical study (P106, n=13) was performed to determine the relative bioavailability of the new paediatric formulation (PFS), relative to the tablet formulation (marketed) in healthy adult. In addition, the effect of food on POS PK administered as PFS was also investigated.

PK results indicate that the extent of exposure (AUC0-72) was 19% higher with the PFS compared to the tablet formulation with GMR of 1.19 (90% CI 1.10-1.28). Results remain similar for Cmax with a GMR of 1.17 (90% CI 1.04-1.33) for PFS compared to tablet. Both 90% CI fell outside the 0.8-1.25 BE limits.

Under fed conditions for PFS, only Cmax was moderately impacted (23 to 41% decrease) whereas AUC0-72 remain similar. Therefore, the recommendation that PFS can be administered with or without food is acceptable.

2.6.2.4. Pharmacokinetics in target population

This extension of the indications of POS in the paediatric population, aged 2 to < 18 years included one PPK analysis. This analysis was performed following the results from Study P097.

- Study P097

Design

This was a non-randomized, multicentre, open-label, sequential dose-escalation study designed to evaluate the safety, tolerability and PK of the IV and PFS formulations of POS in paediatric subjects with actual or anticipated neutropenia and who were at risk for developing IFI.

118 subjects between the ages of 2 to < 18 years were enrolled and divided in two groups (2 to < 7 years and 7 to < 18 years). Three POS dose levels were assessed, 3.5 mg/kg, 4.5 mg/kg and 6 mg/kg daily.

In each dose cohort, paediatric subjects received POS IV BID on Day 1, then QD on Days 2 to 10. Thereafter subjects received POS PFS QD or continued on IV if they were unwilling or unable to tolerate POS PFS.

The maximum total duration of treatment was 28 days. The maximum dose was set to 300 mg. Steady state POS plasma concentration profiles based upon rich PK sampling were obtained after 7 to 10 days of dosing of each formulation.

PK sampling

For both formulations, after 7 to 10 days of continuous dosing steady-state POS plasma concentrations were determined at pre-dose, 2, 4, 6, 8, and 24 hours post administration.

Results

Of the 118 enrolled subjects, 115 subjects started on IV treatment and 15 of those were not included in the PK analysis. Reasons for exclusion from the IV PK were PK concentrations not obtained (9/15), dose was not given within 6h of scheduled time (5/15), and PK outlier (1/15).

Of 63 subjects who transitioned to the PFS treatment and received at least one PFS dose, 13 were not included in the PK analysis. Reasons for exclusion were PK data not obtained (10/13) and incomplete PFS dose taken (3/13).

Non-compartmental PK analysis

A summary of mean PK parameters based on NCA by dose cohort, age group, and formulation is presented in Table 11.

Table 11: Summary of POS plasma SS PK parameters values following multiple dose of IV or PFS formulations

Dose Cohort	Age Group	Formulation	n	Cmax (ng/mL)[a]	Tmax (hr)[b]	AUC0-24 (hr*ng/mL)[a]	C0 (ng/mL)[a]	Cmin (ng/mL)[a]	Cavg (ng/mL)[a]
3.5 mg/kg	2 to <7 yrs old	IV	11	1590 (43.1)	1.78 (1.67 - 5.53)	17800 (55.0)	424 (81.3)	400 (81.3)	743 (55.0)
		PFS	5	884 (44.4)	3.83 (1.92 - 4.25)	12200 (36.0)	261 (40.7)	254 (45.6)	510 (36.0)
	7 to <18 yrs old	IV	19	2450 (72.7)	1.77 (0.00 - 3.50)	27300 (49.7)	802 (90.4)	670 (65.1)	1140 (49.7)
		PFS	10	1340 (30.8)	2.20 (1.92 - 6.03)	20700 (33.8)	629 (46.5)	579 (44.9)	861 (33.8)
4.5 mg/kg	2 to <7 yrs old	IV	14	2320 (39.8)	1.78 (1.42 - 5.90)	25600 (30.0)	542 (60.2)	501 (56.8)	1070 (31.3)
		PFS	8	1550 (40.8)	3.82 (1.88 - 5.92)	21600 (64.5)	616 (151.9)	476 (164.6)	901 (64.5)
	7 to <18 yrs old	IV	15	2310 (40.3)	1.75 (1.52 - 1.80)	29800 (42.9)	824 (62.8)	737(66.0)	1240 (42.9)
		PFS	8	1670 (28.5)	6.14 (1.98 - 7.98)	28700 (33.7)	827 (54.3)	790 (48.2)	1200 (33.7)
6.0 mg/kg	2 to <7 yrs old	IV	17	3060 (54.1)	1.75 (1.57 - 1.83)	31100 (48.9)	697 (98.2)	626 (104.8)	1300 (48.9)
		PFS	7	1510 (43.4)	4.00 (2.17 – 7.92)	23000 (47.3)	593 (82.8)	542 (68.8)	960 (47.3)
	7 to <18 yrs old	IV	25	3340 (39.4)	1.77 (1.33 - 6.00)	44200 (41.5)	1290 (53.5)	1160 (60.4)	1840 (41.5)
		PFS	12	1370 (178.5)	2.78 (0.00 - 4.00)	25000 (184.3)	902 (141.8)	713 (300.6)	1040 (184.3)

AUC0-24 – Area under plasma concentration-time curve from 0-24 h; C0 – Pre-dose plasma concentration; Cavg - Average plasma concentration over the dosing interval at steady state; Cmax – Peak plasma concentration; Cmin – Plasma concentration 24 hr postdose; Tmax – Time to peak concentration;
[a]Geometric mean (%GCV)
[b]Median (Min - Max).

The CHMP noted that, for the 6 mg/kg dose cohort, for both age groups (2-<7 years and 7 to <18 years), Cmax,ss was approximately twice greater with IV compared to PFS (3060 vs 1510 ng/mL and 3340 vs 1370 ng/mL).

In contrast to the other dose cohort (3.5 and 4.5 mg/kg) where Cavg,ss appears generally similar between IV and PFS within each age group, for the 6 mg/kg dose cohort, such trend is not observed.

Target attainment (PK bridging)

The exposure target specified in the protocol for the IV and PFS formulations was to identify a dose regimen that would result in a geometric mean Cavg of ~ 1200 ng/mL with approximately 90% of subjects having Cavg between 500 and 2500 ng/mL. These targets were discussed and agreed by FDA and PDCO.

Bearing in mind these targets, Table 12 presents the observed PK target attainment. Overall Cavg data calculated by NCA indicate that the PK targets were not attained for the 3.5-mg/kg per day dose group. The PK targets were generally achieved for the 4.5- and 6.0-mg/kg per day dose levels for each age group and formulation. The higher exposure observed overall for the 6 mg/kg per day dose increases the proportion of subjects with posaconazole concentrations exceeding a value of 500 ng/mL associated with efficacy even at the end of the dosing interval (i.e., Cmin) while remaining within the typical concentration range over which safety data have been obtained.

Table 12: Percent of subject below, within and above the specified Cavg PK target range following multiple dose of IV and PFS formulations in paediatric subjects.

Dose	Age Group	Formulation	n	Number of subjects (%) with Cavg <500 ng/ml	Number of subjects (%) with Cavg 500 – 2500 ng/mL	Number of subjects (%) with Cavg >2500 ng/mL
3.5 mg/kg	2 to <7 yrs old	IV	11	2 (18%)	9 (82%)	0
		PFS	5	3 (60%)	2 (40%)	0
	7 to <18 yrs old	IV	19	0	18 (95%)	1 (5%)
		PFS	10	1 (10%)	9 (90%)	0
4.5 mg/kg	2 to <7 yrs old	IV	14	0	14 (100 %)	0
		PFS	8	1 (13%)	7 (88%)	0
	2 to <18 yrs old	IV	15	0	14 (93%)	1(7%)
		PFS	8	0	8 (100%)	0
6.0 mg/kg	2 to <7 yrs old	IV	17	0	15 (88%)	2 (12%)
		PFS	7	0	7 (100%)	0
	7 to <18 yrs old	IV	24	0	18 (75%)	6 (25%)
		PFS	12	2(16%)	8 (67%)	2 (16%)

Cavg= Average plasma concentration over the dosing interval at steady state; IV = Solution for injection/concentration for solution for infusion; n=number of subjects; PFS=Powder for oral suspension

Dose was scaled by BW up to a maximum total dose of 300 mg, the recommended adult dose for both IV and oral tablet formulation. The BW above which subjects received 300 mg were 85.7, 66.7 and 50 kg respectively for the 3.5, 4.5 and 6 mg/kg dose cohort. Individual and geometric mean Cavg for the 6 mg/kg per day dose for each formulation and age group as a function of BW is shown in Figure 2. Subjects to the right of the vertical line received the maximum dose of 300 mg/day. Overall these plots show no obvious relationship between Cavg and BW particularly at 6 mg/kg per day, which supports the conclusion that the weight-based dosing approach used in Study P097 is appropriate.

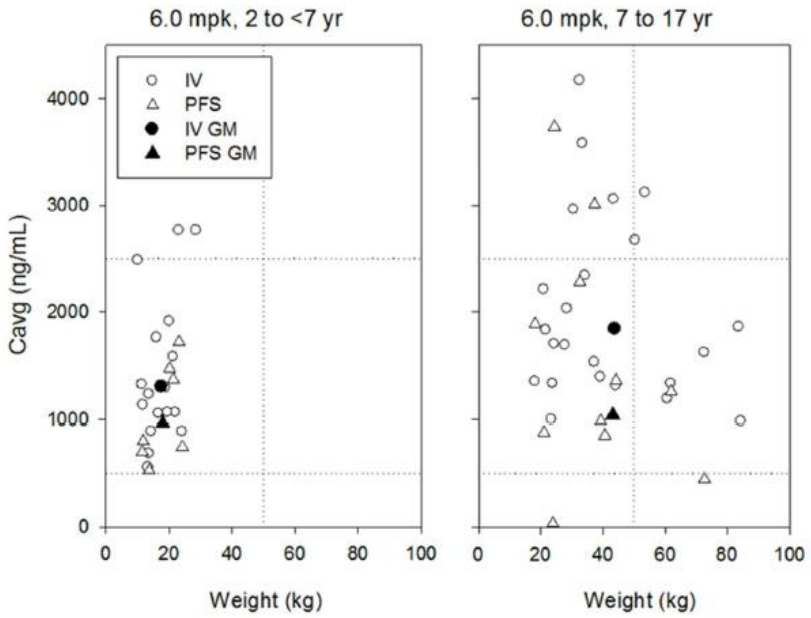


Figure 2: Individual and geometric mean plasma SS Cavg values of POS following multiple dose IV and oral PFS administration of POS 6 mg/kg per day up to a maximum dose of 300 mg

The CHMP noted that the PK target (mean Cavg of ~ 1200 ng/mL with approximately 90% of subjects having Cavg between 500 and 2500 ng/mL) was mainly attained with the 4.5 mg/kg dose cohort, except for the IV and PFS group from low age (2 to < 7years) with Cavg below the 1200 ng/mL threshold.

In contrast for the 6 mg/kg age group, except several subjects which were over-exposed with Cavg > 2500 ng/mL (n=7), and one outlier with particularly low exposure (PFS, < 500 ng/mL), the 1200 ng/mL threshold was not attained.

Population Pharmacokinetic model

Model development

The analysis was conducted using data from study P097 only. The concentration-time data for POS were modelled using a compartmental approach. Log transform PK data was considered.

Covariates of interest of POS investigated were body weight (BW), body surface area (BSA), age, body mass index (BMI), gender, race, ethnicity, food status, estimated glomerular filtration rate, formulations.

The PopPK model was built using nonlinear mixed effects model with the first order conditional estimation method (FOCE) in Nonmem 7.2. Since previous analysis of POS IV and PFS PK data in paediatric have used a 1 cpt model with first order absorption, a more complex model was not investigated.

Except BW as used as part of the structural PK mode using allometric scaling, the other covariates were tested using a stepwise/backward selection procedure. Then the PopPK model was evaluated using a pcVPC.

In addition, in order to evaluate the final PK model, exposure parameters as Cavg and Cmin were derived from the post hoc EBE and compared to the available from NCA analysis.

Then a simulation exercise was performed to simulate the distribution of POS exposure in both age groups, in order to derive the following metrics (Cavg and Cmin) at specified time points (Day 10 and

Day 28) under three dosing regimens (4.5, 6, 7.5 mg /kg) with a maximum absolute dose of 300 mg. The goal was to evaluate whether these dosing regimens for each route/formulation and without regards to meal provide exposures in each group that are associated with POS efficacy.

Results

The analysis dataset included 1236 observations from 114 paediatric subjects aged 2 to 17 years. In total, 80 samples were excluded from the analysis. Of these, two subjects were excluded from the analysis because of incomplete oral PFS dose intake (33 samples). For 31 observations, sampling time was not available. Furthermore, 13 samples had the same sampling time and were excluded as well.

Figure 3 presents POS plasma concentrations in the log transformed scale by age subpopulation and dose regimen. **Table *13*** presents summary of covariates.

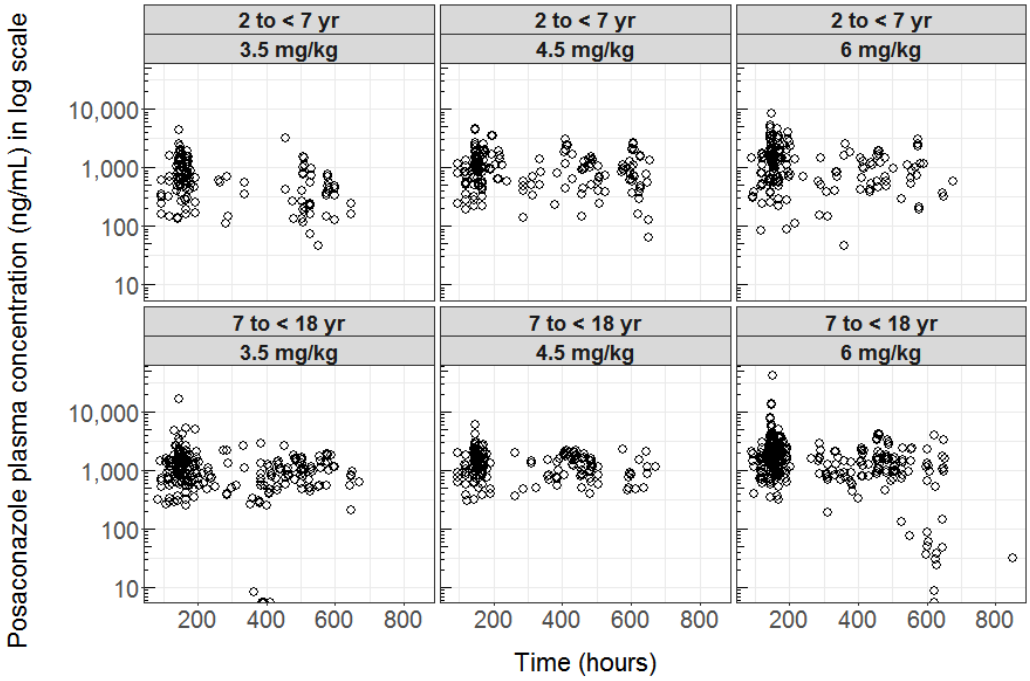


Figure 3: POS plasma concentration per dose and age cohort

Table 13: Summary of continuous and categorical covariates

Covariate	Age group	Min	Median	Max	N	Missing
Age (years)	2-<7 years	2	3	6	48	0 (0.0%)
	7-17 years	7	13	17	66	0 (0.0%)
	All	2	8	17	114	0 (0.0%)
BMI	2-<7 years	12.8	15.5	30.7	47	1 (2.1%)
	7-17 years	12.6	18	33.7	65	1 (1.5%)
	All	12.6	16.5	33.7	112	2 (1.8%)
BSA (m2)	2-<7 years	0.475	0.662	1.1	47	1 (2.1%)
	7-17 years	0.793	1.39	2.26	65	1 (1.5%)
	All	0.475	1.02	2.26	112	2 (1.8%)
eGFR (mL/min/1.73m2)	2-<7 years	55.3	154	399	47	1 (2.1%)
	7-17 years	12.2	138	314	65	1 (1.5%)
	All	12.2	146	399	112	2 (1.8%)
Heigh (cm)t	2-<7 years	81.6	102	130	47	1 (2.1%)
	7-17 years	114	156	195	65	1 (1.5%)
	All	81.6	132	195	112	2 (1.8%)
Weight (kg)	2-<7 years	10.2	16	41.7	48	0 (0.0%)
	7-17 years	18.2	45.4	102	66	0 (0.0%)
	All	10.2	28.6	102	114	0 (0.0%)

Covariate	Category	N	%N	Missing
Sex	Female	47	41.2	0 (0.0%)
	Male	67	58.8	0 (0.0%)
Ethnicity	Hispanic or Latino	15	13.2	0 (0.0%)
	Not Hispanic or Latino	99	86.8	0 (0.0%)
Race	Asian	11	9.65	0 (0.0%)
	Multiracial	4	3.51	0 (0.0%)
	Native Hawaii	1	0.877	0 (0.0%)
	Black	3	2.63	0 (0.0%)
	White	95	83.3	0 (0.0%)

Key steps of the PK structural model were provided. The base and final PK model (after exclusion of 3 outliers concentration with CWRES > 6) consists of 1 cpt PK model from which PK parameters estimates are provided in Table 14 and associated GOF in Figure 4.

Table 14: Key steps in development of structural PK model

Run number	Reference run	Description	OFV	dOFV
100		1 Compartment model with IIV on CL and V_c	-23.527	
101	100	1 Compartment model with IIV on CL, V_c and F1	-599.813	-576.286
201	101	+ Correlation between CL and V_c	-665.348	-65.535
303	201	+ Weight on CL and V_c (power fixed to 0.75 and 1 respectively)	-755.286	-89.938
306	201	+ Weight on CL and V_c (estimated powers)	-762.944	-97.596
606	306	+ Estimated F1	-773.729	-10.785
906	606	+ Estimated F1 (logit function)	-773.652	0.077
1000	906	Excluded outliers	-952.219	-178.567

.

The final base structural model was a one-compartment model with first order absorption, IIV on CL, Vc and F1, correlation between CL and Vc, estimated allometric exponent on CL and Vc, estimated F1 using a logit function and an additive error model in the logarithmic scale. All model parameters were well estimated, with RSE% values < 10% for the fixed effect parameters and <25% for the random effect parameters (Table 15). Estimates of the allometric exponents for body weight effects on CL and Vc (0.626 and 0.963, respectively) approximated theoretical values (0.75 and 1, respectively). Eta-shrinkage was low on CL (7%) and particularly high for both Vc and F1 (28 and 42% respectively).

Overall the GOF plots presented in Figure 4 indicate that the structural PK model provide an adequate description of POS concentration time data, with no clear bias.

Table 15: Final PK parameter estimates

Parameter	Estimate	RSE(%)	Shrinkage (%)
CL (L/h)	4.71	3.86	
V_c (L)	112	5.18	
KA (h^{-1})	0.212	17.9	
F1	0.826	5.58	
α for CL	0.624	9.86	
α for V_c	0.971	7.86	
IIV (CL)[a]	37.1	8.15	5
IIV (V_c)[a]	27.7	24.75	34
IIV (F1)[b]	2.02	18.9	42
Residual error (SD)	0.331	4.71	8

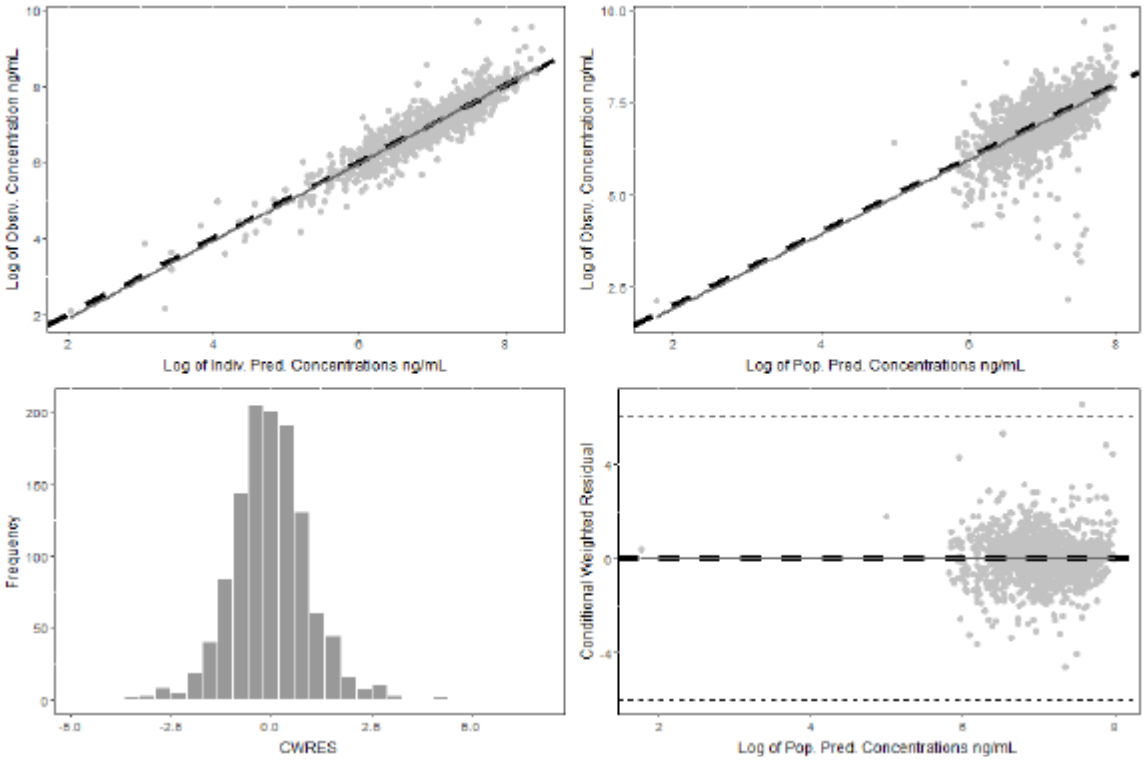


Figure 4: GOF of the Final PK model

As BW was part of the structural PK model (with estimated allometric exponents), age, EGFR, sex and ethnicity effects were investigated on CL and V. Food effect was tested on F1.

The potential effect of food on the bioavailability of POS PFS was assessed after completion of the stepwise covariate analysis (SCM). Food intake was captured through different covariates, an overview of which is included in Table 16. These different covariates captured information on food intake within 2 hours prior to or up to 1 hour after the associated dose administration. In addition to the more granular covariate categorizations capturing the specific pre- or post-dose timing as well as meal content, an overall food covariate was created (FOOD) which described whether the dose administration was associated with any type of food intake between 2 hours prior to and 1 hour after the dose administration.

Table 16: Description of food covariates tested after SCM analysis

Covariate code	Covariate definition	Category definition	Number of subcategories
FOODPR	2 hours predose food intake	No meal, Meal	2
FDTYPEPR	2 hours predose food intake	No meal, Light Meal, Medium Meal, Heavy Meal	4
FOODPO	1 hour postdose food intake	No meal, Meal	2
FDTYPEPO	1 hour postdose food intake	No meal, Light Meal, Medium Meal, Heavy Meal	4
FOOD	2 hours predose and 1 hour postdose food intake	No meal, Meal	2
FDTYPE	2 hours predose and 1 hour postdose food intake	No meal, Light Meal, Medium Meal, Heavy Meal	4

Results of this analysis are provided in Table 17 below. For most of the food effect covariates, the inclusion of the covariate on F1 did not result in a statistically significant improvement in the fit of the population PK model per the defined criteria for covariate selection (P<0.01 as reflected by a decrease

in OFV of at least 6.63 for the addition of 1 parameter, or at least 11.345 for the addition of 3 parameters). For the 4-category overall food effect parameter, a statistically significant difference in OFV (-12.2) was observed; however, the food effect parameters were estimated with low precision (RSE > 50%), and therefore the effect was not maintained in the final model. Therefore, the final structural model without food effects is considered as the final model.

Table 17: Overview of model tested with food effect covariate on F1

Model	Reference Model	Description	Number of added parameters	OFV	dOFV
1000		Final model		-952.22	
1003	1000	Overall food effect on Bioavailability: Meal versus no Meal (FOOD)	1	-957.01	-4.79
1006	1000	Overall food effect on Bioavailability: No vs Light vs Medium vs Heavy meal (FDTYPE)	3	-964.4	-12.2
1009	1000	Pre-dose food effect on Bioavailability: Meal versus no Meal (FOODPR)	1	-953.94	-1.72
1010	1000	Pre-dose food effect on Bioavailability: No vs Light vs Medium vs Heavy meal (FDTYPEPR)	3	-957.86	-5.64
1011	1000	Post-dose food effect on Bioavailability: Meal versus no Meal (FOODPO)	1	-952.96	-0.74
1012	1000	Post-dose food effect on Bioavailability: No vs Light vs Medium vs Heavy meal (FDTYPEPO)	3	-963.27	-11.1

pcVPC are provided in Figure 5 (all data) and in Figure 6 split per age and formulations. Overall predictive performance are acceptable except for the 5th percentile which is probably attributable to low simulated values of F1, producing concentrations that are lower to those observed in the data.

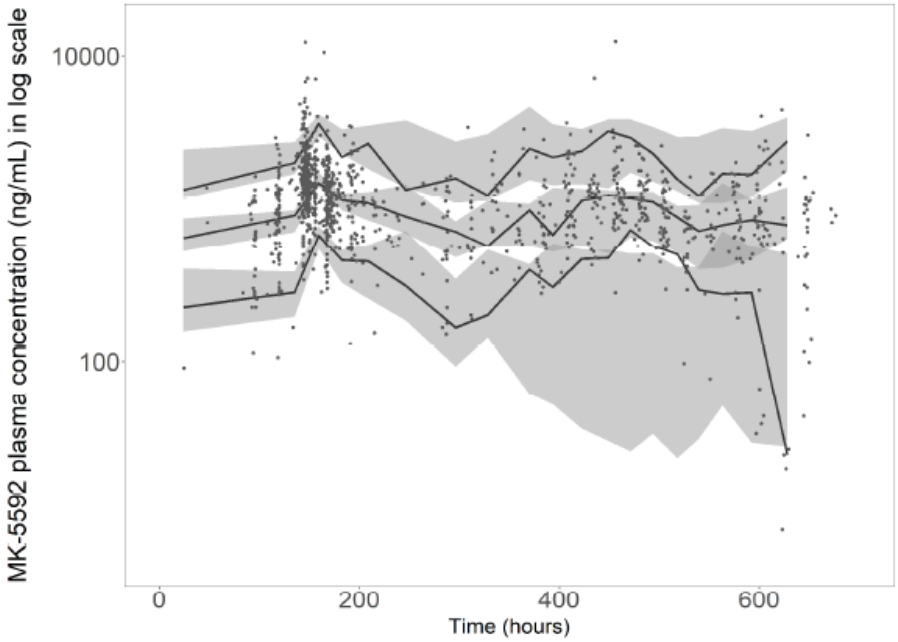


Figure 5: pcVPC on the full data

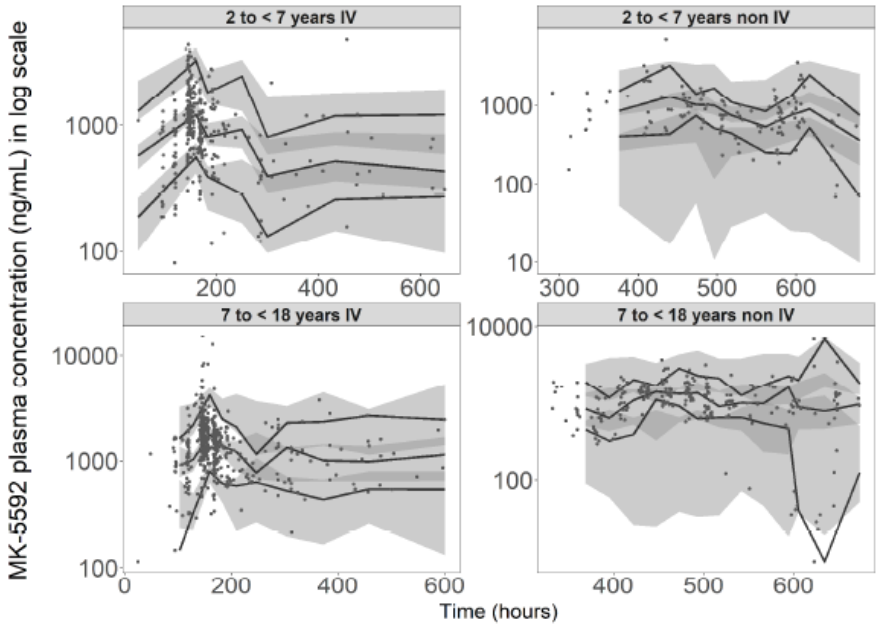


Figure 6: pcVPC split per age cohort and formulations

Comparison between observed and predicted PK parameters

Cavg and Cmin, respectively estimated and observed by NCA were compared to those predicted by the PPK model. Results are display in Figure 7 and Table 18.

In general, Cavg and Cmin values after both IV and oral PFS administration approximate the identity line (black dashed line) for each of the included dose levels (3.5, 4.5 and 6 mg/kg), showing that the popPK model is able to reproduce adequately the exposure parameters derived from the NCA analysis. Distributions of prediction errors for Cavg and Cmin derived from the PopPK analysis in comparison to those from the NCA analysis were summarized by the MAH. More than 80% of the individual Cavg estimates from the PopPK are less than 20% different from the NCA-derived values. For Cmin, since based on a single concentration value per individual, deviations between the estimates from the two methods were somewhat larger, with up to 20% of estimates being more than 50% different. Overall, even though some discrepancies were observed between NCA and PopPK model derived exposure parameters, these were not indicative of any particular trend of a bias with dose or route of administration.

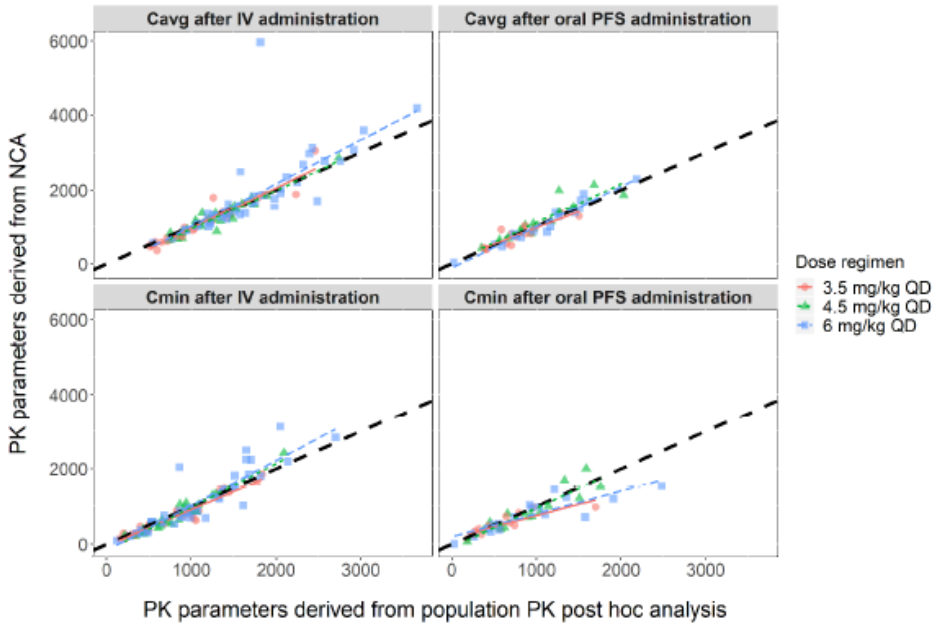


Figure 7: Correlation between PK parameters (Cavg and Cmin) derived from EBE post-hoc and NCA per dose regimen and formulations

Table 18: Proportion of Cavg and Cmin with a relative error (RE) below 20% and 50% for each administration route and dose regimen

Parameter	Dose	RE below 20%	RE below 50%
Cavg after IV administration	3.5 mg/kg	86.21	96.55
	4.5 mg/kg	85.19	96.3
	6 mg/kg	80.95	97.62
Cavg after oral PFS administration	3.5 mg/kg	80	100
	4.5 mg/kg	86.67	100
	6 mg/kg	82.35	100
Cmin after IV administration	3.5 mg/kg	58.62	89.66
	4.5 mg/kg	62.96	96.3
	6 mg/kg	59.52	88.1
Cmin after oral PFS administration	3.5 mg/kg	50	85.71
	4.5 mg/kg	33.33	93.33
	6 mg/kg	52.94	76.47

Simulation

PK profiles for dose regimens of 4.5, 6 or 7.5 mg/kg BID IV dosing on Day 1 followed by QD IV up to Day 10 followed by QD oral PFS through Day 28 were simulated. Total dose was limited to 300 mg or less to avoid any paediatric dose that exceeded that approved for adults (300 mg). Steady-state exposure parameters (Cavg, Cmin) were calculated after the last dosing of IV and PFS and the proportion of subjects achieving the target exposures were determined. Distributions of Cavg and Cmin are also summarized in Table 19. Additionally, geometric mean Cavg and Cmin per dose, formulation and age group are summarized in Table 20.

Table 19: Proportion of subjects achieving specific ranges of simulated Cavg and Cmin at a dose regimen of 4.5, 6 or 7.5 mg/kg QD per age group

Parameter		2 to < 7 years old Concentration ranges (ng/mL)			7 to 17 years old Concentration ranges (ng/mL)		
		4.5 mg/kg			4.5 mg/kg		
		< 500	≥500 to < 2500	≥ 2500	< 500	≥500 to < 2500	≥ 2500
Cavg (%)	IV	2.8	95.6	1.6	0.8	93.4	5.8
	PFS	17.2	82.1	0.7	7.6	89.9	2.5
Cmin (%)	IV	45.3	54.6	0.1	20.7	78.2	1.1
	PFS	48.2	51.5	0.3	23.9	75.2	0.9
		6 mg/kg			6 mg/kg		
Cavg (%)	IV	0.2	94.4	5.4	0.1	82.2	17.7
	PFS	6.8	91.2	2	3.1	89.1	7.8
Cmin (%)	IV	30.2	69.1	0.7	9.7	85.9	4.4
	PFS	30.9	67.9	1.2	14.1	83.2	2.7
		7.5 mg/kg			7.5 mg/kg		
Cavg (%)	IV	0	83.2	16.8	0	70.2	29.8
	PFS	2.9	89.3	7.8	1.9	82.1	16
Cmin (%)	IV	20.8	77.7	1.5	6.4	85.4	8.2
	PFS	20	78.1	1.9	9.7	84.2	6.1

As expected the proportions of Cavg above the target of 500 ng/mL were lower with oral than with IV administration in line with the bioavailability estimate of ~83% for the PFS administration.

Table 20: Predicted geometric mean Cavg and Cmin at a dose regimen of 4.5, 6 and 7.5 mg/kg QD per age group

Parameter		2 to < 7 years old		7 to 17 years old	
		Geometric mean (ng/mL)	Geometric CV (%)	Geometric mean(ng/mL)	Geometric CV (%)
		4.5 mg/kg		4.5 mg/kg	
Cavg	IV	1044.94	40.34	1361	41.98
	PFS	796.61	50.53	1041.55	51.96
Cmin	IV	515.44	70.17	795.48	64.06
	PFS	504.96	65.77	734.8	63.39
		6 mg/kg		6 mg/kg	
Cavg	IV	1364.6	39.18	1748.46	40.66
	PFS	1049.68	50.36	1331.39	51.33
Cmin	IV	656.24	69.65	1035.21	61.37
	PFS	654.95	65.66	947.19	62.21
		7.5 mg/kg		7.5 mg/kg	
Cavg	IV	1713.79	39.65	2001.55	41.54
	PFS	1320.77	50.85	1546.59	53.08
Cmin	IV	830.09	70.76	1210.21	57.99
	PFS	827.78	67.18	1114.93	61.66

Geometric mean Cavg are predicted to be above or around the target concentration of 1200 ng/mL at the dose regimens of 6 mg/kg and 7.5 mg/kg in both age groups and for both IV and PFS administrations.

Overall, the simulation results for PFS and IV administration show that the dosing regimens of both 6 mg/kg and 7.5 mg/kg achieve the required steady-state Cavg values (specifically, greater than 500

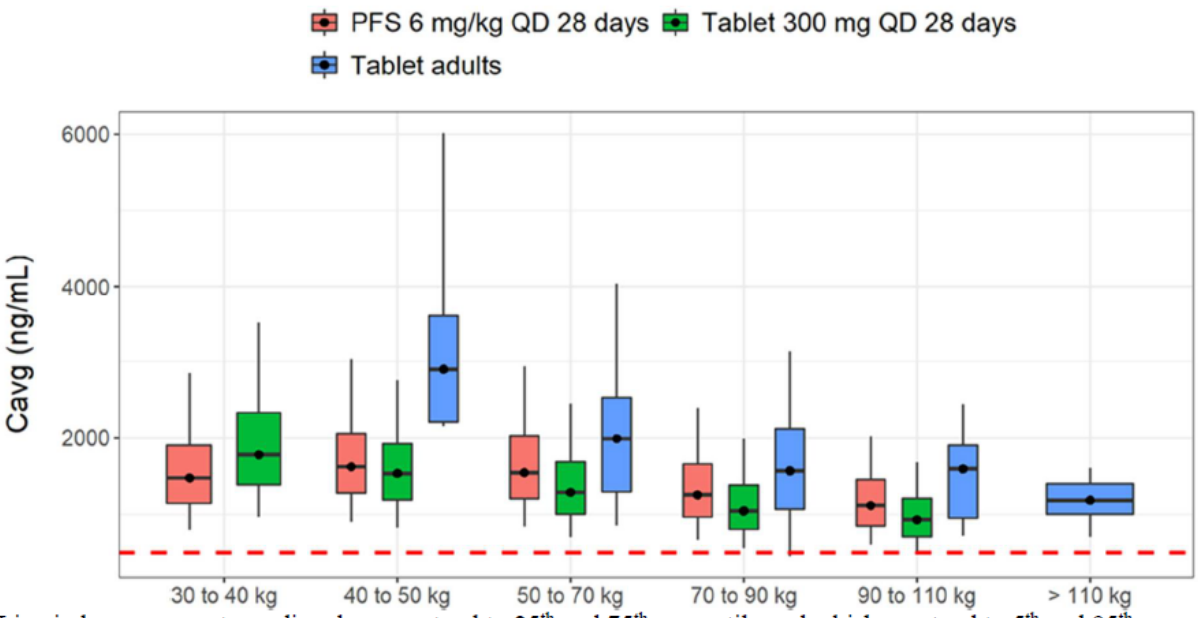
ng/mL for more than 90% of subjects) in both age group populations, irrespective of the route of administration.

Simulation of tablet vs PFS dosing regimens

For POS tablets 300 mg/day, model-predicted Cavg achieved the PK target of Cavg > 500 ng/mL in 90% of subjects across the entire weight range is presented in Table 21. The distribution of model predicted Cavg shifted lower with increasing weight as shown in Figure 8. Compared to PFS, model predicted Cavg for the tablet was 20% lower for cohorts with body weights greater than 50 kg where the tablet and PFS dose were both 300 mg. This reflects the relative bioavailability (PFS/tablet = 1.2) of the 2 formulations. For 40 to 50 kg body weight cohort, model-predicted Cavg was similar between the tablet and PFS formulations and for the 30 to 40 kg cohort, model predicted Cavg was higher for tablet compared to PFS. These results reflect the fixed 300 mg dose for tablet and weight-based 6 mg/kg dose for PFS in these weight ranges.

Table 21: Percent of subjects with Cavg below, within and above the POS Cavg target range by BW for POS tablet and PFS in virtual subjects vs tablet in Adult Ph1B/3 study

Weight categories	Percentage of patients with Cavg:								
	300 mg tablet - Pediatric			POS PFS 6 mg/kg (up to 300 mg) Pediatric			300 mg tablet - Adults (P05615)		
	< 500 ng/mL	≥ 500 to < 2500 ng/mL	≥ 2500 ng/mL	< 500 ng/mL	≥ 500 to < 2500 ng/mL	≥ 2500 ng/mL	< 500 ng/mL	≥ 500 to < 2500 ng/mL	≥ 2500 ng/mL
30 to 40 kg	0.10%	80.10%	19.80%	0.30%	89%	10.70%	--	--	--
40 to 50 kg	0%	90.90%	9.10%	0%	87.80%	12.20%	0%	50%	50%
50 to 70 kg	0.60%	95.30%	4.10%	0.10%	88.10%	11.80%	1.33%	72%	26.67%
70 to 90 kg	2.90%	96%	1.10%	0.50%	95.80%	3.70%	7.62%	80.95%	11.43%
90 to 110 kg	5%	94.60%	0.40%	1.40%	96.60%	2%	0%	96.88%	3.12%
> 110 kg	Not determined						0%	100%	0%



Line in box represents median, boxes extend to 25th and 75th percentile and whisker extend to 5th and 95th percentile. Dashed line represents 500 ng/mL target concentration. Adult tablet data for 300 mg QD (BID on first day) come from P05615

Figure 8: Distribution of model-predicted Cavg by BW for POS tablet and PFS in virtual paediatric subjects vs observed distribution of Cavg for POS tablet in adults

PPK model

The CHMP considered that the PPK model presented by the MAH is based on PK data from N=114 paediatric subjects from which n=1236 PK samples were available. Then, according to the MAH 80 samples were excluded for various acceptable reasons, and of these 2 subjects were excluded. Finally, during the model building several outliers were excluded, n=3. Therefore, based on this information it is expected N=112 paediatric subjects with n=1153 PK samples. However, based on the control stream, N=112 subjects with n=1187 PK observations were considered.

The PPK model consisted of 1 cpt PK model parameterized in terms of CL, Vc, ka and F1. BW allometric scaling with estimated exponents (0.624 and 0.963 for CL and Vc) were considered. Ka was fixed, CL, Vc and F1 were estimated at 4.71 L/h, 112 L and 0.826, respectively with moderate IIV for CL and Vc (37.1 and 27.7 %), and particularly high for F1 (202%). Eta-shrinkage is acceptable for CL only (7%).

The effect of food, investigated on F1 with eta-shrinkage of 47% is questioned. Any output of this analysis should be considered with cautions.

Overall PK parameters were estimated with a good precision, GOF does not show a particular bias and pcVPC shows reasonably adequate predictive performance (except for the 5th percentile).

Cavg and Cmin, NCA vs PPK

Compared to Cavg estimated by NCA, Cavg predicted by the PPK model for both formulations and for both age group remain reasonable (more than 80% with RE below 20%). However, the PPK model seems to over-predict Cmin with PFS mainly for the 6 mg/kg dose cohort.

Simulation

1) PK target attainment

Result of the first simulation exercise show that the use of a 6 mg/kg dose fulfill the PK target of >90% of Cavg between 500 and 2500 ng/mL.

Nevertheless, it should be noted that in the 2-<7 years aged group, a low but non negligible risk of 6.8% of virtual paediatric patients are predicted to have a Cavg below 500 ng/mL with the proposed 6 mg/kg dose with the PFS formulation. Whereas with 7.5 mg/kg dose which have never been tested in the paediatric population it is predicted a risk of 2.9% with Cavg below 500 ng/mL associated to an inflated risk of over-exposure for both formulation (> 2500 ng/mL).

However, based on a Cmin target which can be considered as a more conservative PK parameter, which is currently used in clinical practice using TDM, there is a high risk of 30% and 20% of under-exposure with the 6 mg/kg and 7.5 mg/kg dose respectively. This was identified as a concern, bearing in mind the EUCAST recommendation to target a Cmin of 700 ng/mL for prophylaxis and 1000 ng/mL for the treatment of IFD. This particularly questioned the use of a systematic TDM for POS and required a thorough discussion regarding if an increased dose per kg was warranted in the lower weight groups. [Q56 and 57 or D150]

2) Tablet vs PFS dosing regimens

Result of the simulation exercise support the use of a 300 mg dose for paediatric patient over a BW of 40 kg for both PK target attainment and practical dosing administration (maximum dose delivery of the PFS kit of 240 mg). However, the CHMP considered that the MAH had not adequately presented the exposure in the youngest/lowest weight patients as the boxplots were only down to 30 kg. To this end boxplot and corresponding tables for paediatrics under 30 kg, in 5 kg intervals for both Cavg and Cmin were requested.

To address the two requests above, the MAH provided the detailed PK data on the attainment of target trough levels of 700 ng/mL and 1000 ng/mL among participants from Study P097 who were administered a 6 mg/kg PFS dose, e.g. the observed PK data in patients, and also provided those following the simulation exercise following the 6 mg/kg and 7.5 mg /kg PFS dose.

Values associated with the simulation exercise were presented in Figure 9.

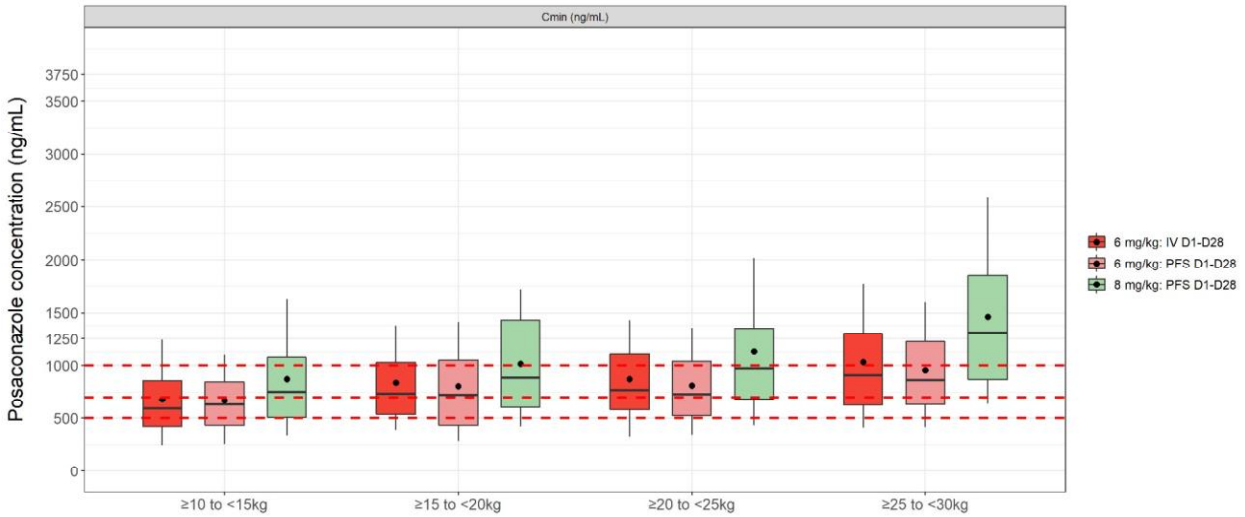


Figure 9 Distribution of Model-Predicted Cmin by Body Weight for Posaconazole IV and PFS in Virtual Paediatric Subjects (Dashed lines represents 500 ng/mL, 700 ng/mL and 1000 ng/mL target concentrations)

Line in box represents median, boxes extend to 25th and 75th percentile and whisker extend to 10th and 90th percentile. Reference lines provided for 500 ng/mL, 700 ng/mL and 1000 ng/mL.

The CHMP noted that the EUCAST targets based on Ctrough cannot be attained at a 6, (7.5) or 8 mg/kg dose as shown in Figure 9. The MAH attributed such "failure" to the higher clearance in younger subjects. Therefore, by considering the fact that the developed PPK fits for purpose, it is expected that the same conclusion can be drawn with the observed PK data in patients (aged 2-7years who were administered a 6 mg/kg PFS dose).

Therefore, instead of targets based on Ctrough, the MAH proposed to use targets based on Cavg, which was acceptable to the CHMP. It is important to note that the EUCAST targets were not used at the time of the PIP submission/modification. In addition, it should be noted that the last recommendation (EUCAST website, Clinical Breakpoints for fungi v10.0 [4 Feb 2020]) rely on a Ctrough target of 1250 ng/mL for curative treatment whereas a 1000 ng/mL target was set in the Clinical Breakpoints for fungi v9.0 [12 Feb 2018]. One also can argue that the Ctrough reported in the EUCAST are not truly a Ctrough (sampled just before the next drug intake) but rather a mean of POS concentration sampled 10 to 24h after drug intake at steady state and at several occasions (given the known prolonged half-life, and consequently the flat typical PK profile of POS).

In order to attain the EUCAST targets (700 ng/mL for prophylaxis or > 1000 ng/mL for curative treatment) based here on Cavg in the paediatric subjects aged 2-7 years, the MAH is now proposing for PFS POS a dosing nomogram, where for subjects weighing 10 to 30 kg or 31 to 40 kg, a dose of 8 mg/kg (a 33% increase in dose) or 6 mg/kg, respectively, is planned to be administered.

Weight (kg)	Dose (volume)
10-13 kg	90 mg (3 mL)
14-17 kg	120 mg (4 mL)
18-21 kg	150 mg (5 mL)
22-25 kg	180 mg (6 mL)
26-30 kg	210 mg (7 mL)
31-35 kg	210 mg (7 mL)
36-40 kg	240 mg (8 mL)

For illustration, by visual inspection for virtual subjects weighing 10 to 15kg, with a 8 mg/kg dose, it is predicted that 50% and less than 25% of the subjects will reach a Ctrough of 700 and 1000 ng/mL respectively. However by considering a Cavg of 700 ng/mL or 1000 ng/mL, approximately more than 75% of the subjects, whatever the weight group, fulfil both targets. More precisely, more than 92% of the subjects weighing 10 to 30 kg are predicted to have a Cavg over 700 ng/mL with a PFS dose of 8 mg/kg.

The proposed 8 mg/kg PFS dose in subjects age 2-7 years and weighing 10 to 30 kg is supported by:

- Predicted Percent of subject with a Cavg < 500 ng/mL similar to that of patients weighing > 30 kg and receiving a 6 mg/kg dose of PFS, all paediatric subjects (2-18 y) receiving a 6 mg/kg dose of the IV formulation, and similar Cavg to that reported in adults following the recommended dose of 300 mg/day (BID Day 1).

- Adequate safety data, with the proposed 8 mg/kg dose, a mean Cavg of 1408 ng/mL is predicted in subjects aged 2-7years and weighing 10-30kg. This predicted Cavg level is covered by the available PK data from paediatric subjects (7-18 y or >30 kg) receiving PFS or IV and by those from the adults receiving tablet or IV POS where comparable or higher exposure were observed.

- The proposed dosing nomogram clearly show that except for subjects weighing 10 to 13 kg where there is approximately a 14% chance of reaching a Cavg less than 700 ng/mL, the proposed 8 mg/kg dose (10 to 30 kg) and 6 mg/kg dose (30 to 40 kg) provide adequate Cavg (less than 14% or 3% of Cavg > 2500 and > 3750 ng/mL, respectively).

- More importantly, there is an overlap between predicted distributions of median (10^{th}-90^{th} percentile) Cavg in subjects weighing 10 -30 kg who were administered PFS at 8 mg /kg (1408 [775-2587] ng/mL, IV at 8 mg/kg (1917 [1198-3116) ng/mL) or weighing 30 to 40 kg who were administered PFS at 6 mg /kg (1341 [718-2401] ng/mL) or IV at 6 mg/kg (1814 [1120-2920] ng/mL) with predicted Cavg in adults who were administered tablets or the IV formulation for prophylaxis 1550 [874-2690] ng/mL and 1890 [1100-3150] ng/mL, respectively. However for treatment of IFI, exposures in the paediatric subjects are generally lower to those from adults.

The CHMP considered the answers from the MAH to be satisfactory.

2.6.2.5. Pharmacodynamics

N/A

2.6.3. Discussion on clinical pharmacology

In support of this extension of indications of posaconazole (POS) in children and adolescent patients from 2 to < 18 years, an additional paediatric formulation (PFS) has been developed to the currently approved ones (solution for infusion and tablet) and tested in a clinical study (P097). Provided PK targets, a PK bridging strategy was performed to support the extrapolation of the indications from adults, using a PPK model.

First a dedicated clinical study (P106) was performed to determine the relative bioavailability of the new paediatric formulation (PFS), relative to the tablet formulation (marketed) in healthy adult. In addition, the effect of food on POS PK administered as PFS was also investigated.

PK results indicate that the extent of exposure (AUC0-72) was 19% higher with the PFS compared to the tablet formulation with GMR of 1.19 (90% CI 1.10-1.28). Results remain similar for Cmax with a GMR of 1.17 (90% CI 1.04-1.33) for PFS compared to tablet. Both 90% CI fell outside the 0.8-1.25 BE limits.

Under fed conditions for PFS, only Cmax was moderately affected (23 to 41% decrease) whereas AUC0-72 remain similar. Therefore, the MAH recommendation that PFS can be administered with or without food is acceptable.

A PPK analysis was performed with only PK data from Study P097 (pooled IV and PFS PK data). A discrepancy between the claimed total PK observations and those used for the PPK analysis, however the issue is not pursued. Overall, the PPK model fit for purpose and is considered adequate to use for simulation.

Two simulation exercises were performed, one to handle the optimal dose to be administered in the paediatric population given the PK bridging target (>90% of subjects with Cavg between 500-2500 ng/mL), and the other one to investigate the predicted PK of POS using the tablet formulation, a

formulation to note which have never been tested in the target population. For this last simulation the MAH set a relative bioavailability F of 1.2 (PFS/tablet =1.2) based on the results from study P106. This assumption is reasonable and is supported.

Result of the first simulation exercise show that the use of a 6 mg/kg dose fulfill the PK target of >90% of Cavg between 500 and 2500 ng/mL.

Nevertheless, it should be noted that in the 2-<7 years aged group, a low but non negligible risk of 6.8% of virtual paediatric patients are predicted to have a Cavg below 500 ng/mL with the proposed 6 mg/kg dose with the PFS formulation. Whereas with 7.5 mg/kg dose which have never been tested in the paediatric population it is predicted a risk of 2.9% with Cavg below 500 ng/mL associated to an inflated risk of over-exposure for both formulation (> 2500 ng/mL).

However, based on a Cmin target which can be considered as a more conservative PK parameter, which is currently used in clinical practice using TDM, there is a high risk of 30% and 20% of under-exposure with the 6 mg/kg and 7.5 mg/kg dose respectively. And this remain a major concern bearing in mind the EUCAST recommendation to target a Cmin of 700 ng/mL for prophylaxis and 1000 ng/mL for the treatment of IFD. To this end it was requested:

a) to provide detailed PK data on the attainment of these targets among participants from study P097 and following the PK simulation exercise for both the 6 mg/kg and 7.5 mg/kg dose. Such PK data (observed PK data) were not provided, only results from the simulation exercise were presented. These results clearly show that the EUCAST targets based on Cmin cannot be reached with a 6 mg/kg or a 8 mg/kg dose. Therefore the MAH proposed to consider EUCAST levels based on Cavg, this could be acceptable.

b) to provide an in-depth discussion on the possibility of increasing the dose per kg in the paediatric subject aged 2 to < 7years. Such discussion was provided and the MAH proposed to increase the PFS up to approximately 8 mg/kg in subjects weighing 10 to 30 kg, while maintaining a 6 mg/kg PFS or IV dose in subjects weighing 30 to 40 kg. To this end for PFS, a dosing nomogram was proposed by the MAH (see below) for subjects weighing from 10 to 40 kg.

Weight (kg)	Dose (volume)
10-13 kg	90 mg (3 mL)
14-17 kg	120 mg (4 mL)
18-21 kg	150 mg (5 mL)
22-25 kg	180 mg (6 mL)
26-30 kg	210 mg (7 mL)
31-35 kg	210 mg (7 mL)
36-40 kg	240 mg (8 mL)

Results of the associated simulations show an overlap between the predicted Cavg in paediatric subjects with those of the predicted exposures in adult subjects who were administered tablets in a prophylaxis context. For a curative treatment, the exposure predicted in the paediatric subjects are lowered compared to those from adults but remain generally over a Cavg of 1200 ng/mL.

Result of the second simulation exercise support the use of a 300 mg dose with the tablet formulation for paediatric patient over a BW of 40 kg for both PK target attainment. However it should be noted that no clinical data in paediatric patients who were administered the tablet formulation are available. Of note, a Phase 2 study (P104) is ongoing to evaluate posaconazole (IV, tablet and PFS) in children 2

years to 17 years of age, as agreed within PIP EMEA-000468-PIP02-12-M06. The MAH is expected to submit PK and clinical data from this study once it is concluded and the report is available.

2.6.4. Conclusions on clinical pharmacology

Overall, the PPK analysis provides an adequate description of posaconazole PK in the paediatric population. The dosing regimen with both the IV/PFS formulation or tablet formulation (for subject >40 kg) is agreed in the 2-17 years age group.

2.6.5. Clinical efficacy

This paediatric extension of indication is based on a bridging strategy. Clinical studies were performed to assess the PK data in the new paediatric population, in order to reach effective and safe posaconazole exposures.

Overall, two clinical studies were performed: study P032 and study P097. First, study P032 was conducted to assess 3 dose levels of the current posaconazole oral suspension (OS) formulation in immunocompromised paediatric subjects aged 3 months through <18 years. However, the PK exposure target was not met with any dose of the OS formulation and the study was terminated early. Thus, a new oral formulation (powder for oral suspension, PFS) was developed for paediatric patients and 3 dose levels were assessed in the study P097, which is considered as the main clinical study for this paediatric extension of indication.

The objective of P097 study was to evaluate PK in children to show that IV formulation (POS IV) and the new oral formulation (POS PFS) can reach effective and safe concentrations. P097 is not an efficacy study and there is no efficacy endpoint. This study has included immunocompromised paediatric subjects with high risk of Invasive Fungal Infections (IFIs). As posaconazole was given for prophylaxis of IFI in this study, the occurrence of AEs consistent with IFI and Day 100 survival were collected, as a surrogate marker of efficacy.

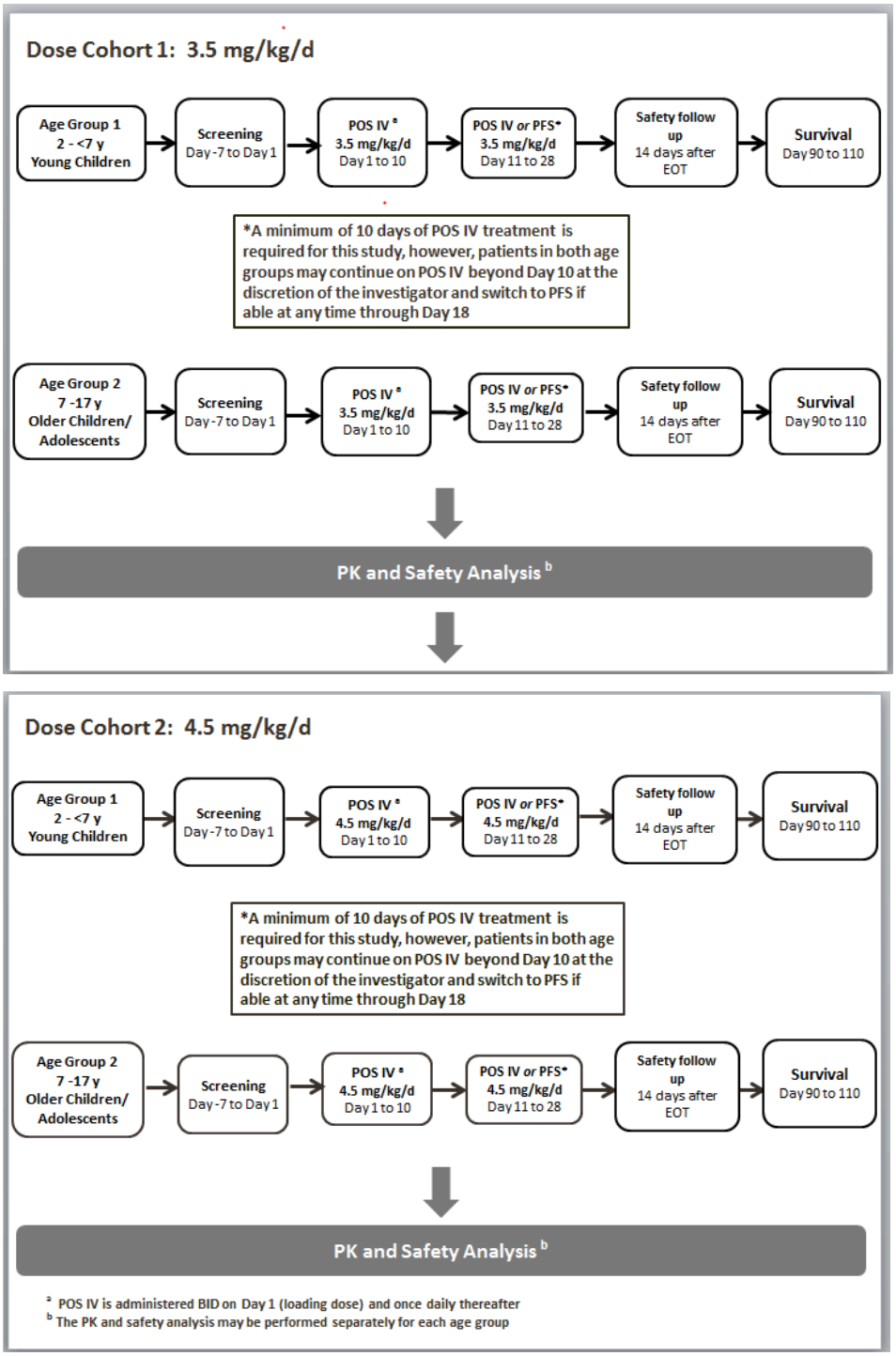
Study Number (Status) [CTD Location] Number of Study Sites (Countries)	Design (Indication)	Number of Subjects by Treatment Group	Study Population (N)	PK Parameters/Results
Phase 1b				
5592-032 (P03579) Completed [Ref. 5.3.3.2: P032] 21 sites (5 countries)	Non-randomized, multicenter, open-label, sequential dose-escalation study of the PK, safety and tolerability of POS oral suspension (OS) when used as prophylaxis in immune-compromised children aged 3 months to <18 years of age at high risk for IFI Duration: approximately 82 months	For all dose cohorts, the maximum total treatment duration was 28 days. **POS OS 12 mg/kg/day PO, divided into 2 doses (BID)** Age Group 1 *(2 to <7 years)*: 22 subjects treated Age Group 2 *(7 to <18 years)*: 21 subjects treated **POS OS 18 mg/kg/day PO, divided BID** Age Group 1: 19 subjects treated Age Group 2: 28 subjects treated **POS OS 18 mg/kg/day PO, divided into 3 doses (TID)** Age Group 1: 15 subjects treated Age Group 2: 30 subjects treated **POS OS 12 mg/kg/day PO, divided TID** Age Group 3 *(3 months to <2 years)*: 1 subject treated **Dose Cohort 3** Day 1: POS 6.0 mg/kg IV BID Days 2-10: POS 6.0 mg/kg IV QD Days 11-20: switch to POS PFS 6.0 mg/kg PO QD or continue POS 6.0 mg/kg IV QD Age Group 1: 20 subjects treated Age Group 2: 29 subjects treated	136 treated subjects: 79 males (58%), 57 females (42%) Median age 8.5 years (range 0.9–17.9 years) Median weight 29.8 kg (range 8.7–104.9 kg)	**PK Parameters:** 1. The following primary PK parameters were estimated for determination of bioavailability comparisons: Cmin, Cmax, Tmax, AUC(tf). 2. For each dose-by-age-group cohort, the target PK exposure for POS was a mean steady-state Cavg exposure of ~1200 ng/mL, with the goal of achieving ~90% of the subjects with Cavg values between 500 and 2500 ng/mL at Day 7. 3. Comparison of the P032 exposure results (from analyses conducted at steady state) with previous results from adult subjects in Study P01899 (use of POS oral suspension in adult subjects). • Proportion of P032 pediatric subjects and P01899 adult subjects with steady-state Cavg ≥500 ng/mL. **P032 PK Results:** 1. None of the age-by-dose cohorts achieved the target exposure of 90% of subjects with a steady-state Cavg between 500 and 2500 ng/mL, resulting in early study termination. • The percentages ranged from 31% of subjects in Age Group 1 receiving 12 mg/kg/day divided BID to 80% of subjects in Age Group 2 receiving 18 mg/kg/day divided TID. • 1 subject in Age Group 3 receiving 12 mg/kg/day divided TID did not meet the target exposure. 3. For both formulations, target PK exposure of ~90% of subjects with a Cavg between 500 and 2500 ng/mL was met in Age Group 1 but not in Age Group 2. 4. Geometric mean Cavg values were higher in Dose Cohort 3 compared with Dose Cohorts 1 and 2.
Abbreviations: AUC = area under the concentration-time curve; AUC(tf) = area under the plasma-concentration-versus-time curve from time 0 to the time of the final quantifiable sample; BID = twice a day; Cavg = average steady-state plasma concentration; Cmax / Cmin = maximum / minimum observed plasma concentration; CL = total body clearance following IV dose; CL/F = apparent total body clearance following oral dose; IFI = invasive fungal infections; IV = intravenous; OS = oral suspension; PFS = powder for oral suspension; PK = pharmacokinetic(s); PO = *per os* (by mouth); POS = posaconazole; QD = once a day; TID = 3 times a day; Tmax = time to maximum observed plasma concentration.				
				2. In Study P01899 the geometric mean Cavg at steady state, and the percentage of subjects who met the target range of Cavg values between 500 and <2500 ng/mL, fell within the P032 range of estimates across Age Groups 1 and 2.
5592-097 Completed [Ref. 5.3.3.2: P097MK5592] 29 sites (11 countries)	Nonrandomized, multicenter, open-label, sequential dose-escalation study of the safety, tolerability, and PK of the POS IV solution and POS powder for oral suspension (PFS) in immunocompromised children and adolescents (2 to <18 years) with neutropenia or expected neutropenia Duration: approximately 36 months	For all dose cohorts, the maximum total treatment duration was 28 days. **Dose Cohort 1** Day 1: POS 3.5 mg/kg IV BID Days 2-10: POS 3.5 mg/kg IV QD Days 11-20: switch to POS PFS 3.5 mg/kg PO QD or continue POS 3.5 mg/kg IV QD Age Group 1 *(2 to <7 years)*: 14 subjects treated Age Group 2 *(7 to <18 years)*: 21 subjects treated **Dose Cohort 2** Day 1: POS 4.5 mg/kg IV BID Days 2-10: POS 4.5 mg/kg IV QD Days 11-20: switch to POS PFS 4.5 mg/kg PO QD or continue POS 4.5 mg/kg IV QD Age Group 1: 15 subjects treated Age Group 2: 16 subjects treated	115 treated subjects: 67 males (58.3%) 48 females (41.7%) Median age 8.0 years (range, 2 to <18 years) Median weight 28.6 kg (range, 10.2–101.6 kg)	**P097 PK Parameters:** 1. PK parameters (Cmax, Cmin, Cavg, Tmax, AUC, CL, CL/F) by POS formulation, dose cohort, and age group: Primary PK parameter: Cavg for both IV and PFS formulation. Exposure target: geometric mean Cavg of ~1200 ng/mL with ~90% of subjects having Cavg between 500 and 2500 ng/mL. **P097 PK Results:** Dose Cohort 1 1. For both IV and PFS formulation, target geometric mean Cavg of ~1200 ng/mL was not met in either age group. 2. For both formulations, target PK exposure of ~90% of subjects with a Cavg between 500 and 2500 ng/mL was met in Age Group 2 but not in Age Group 1. Dose Cohort 2 1. For both formulations, target geometric mean Cavg was exceeded in Age Group 2 and was not met in Age Group 1. 2. For both formulations, target PK exposure of ~90% of subjects with a Cavg between 500 and 2500 ng/mL was met in both age groups. Dose Cohort 3 1. For IV formulation, target geometric mean Cavg was met in both age groups. 2. For PFS formulation, target geometric mean Cavg was not met in both age groups. However, if the single subject with extremely low exposure in Age Group 2 was excluded, then the target was met.

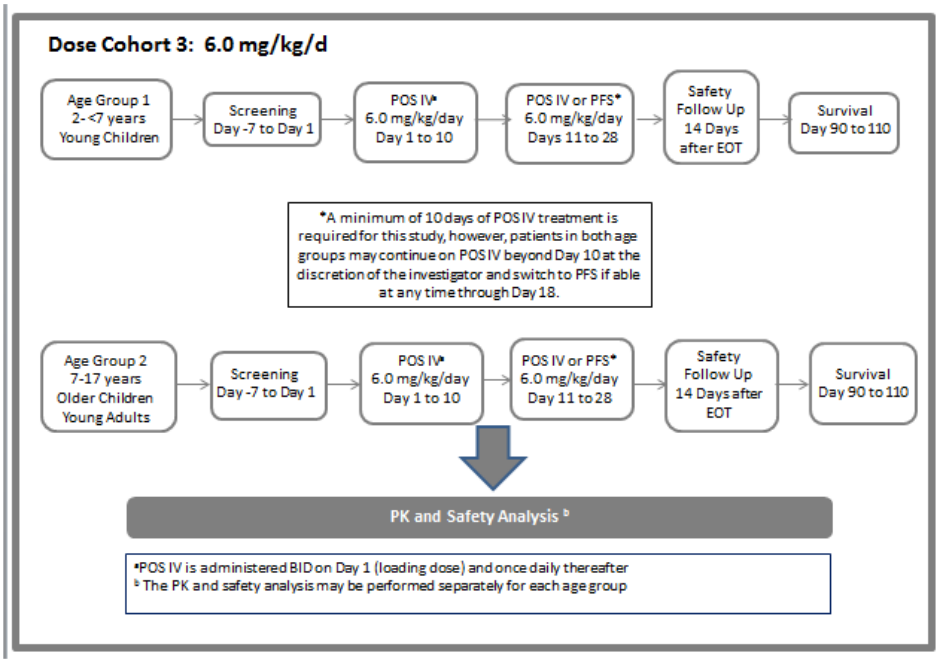
2.6.5.1. Main study

- Study P097

Methods

This is a Phase 1b, non-randomized, multicenter, open-label, sequential dose-escalation study, with 3 doses cohorts (3.5, 4.5 and 6 mg/kg/day):





- **Study Participants**

Inclusion criteria:

Subjects were male or female immunocompromised children between the ages of 2 years to 17 years (inclusive) with documented or anticipated neutropenia (ANC<500/mm3 [0.5 x 10^9/L]) expected to last for at least 7 days following start of study treatment in at least one of the following clinical situations: acute leukemia, myelodysplasia, severe aplastic anemia, recipients of Autologous HSCT, high risk neuroblastoma, advanced stage non-Hodgkin's lymphoma (NHL), recipients of allogeneic HSCT during the pre-engraftment (neutropenic) period, hemophagocytic lymphohistiocytosis.

Subjects must have a central line (e.g. central venous catheter, peripherally inserted central catheter, etc.) in place or planned to be in place prior to beginning IV study therapy.

Exclusion criteria:

The main exclusion criteria were: a proven or probable IFI; a posaconazole treatment within the past 10 days prior to screening; a moderate or severe liver dysfunction; a creatinine clearance < 30 ml/min; a QTc prolongation (symptomatic QTc prolongation >450 msec for males or >470 msec for females, OR any QTc prolongation of >500 msec); pregnancy/breastfeeding; a history of anaphylaxis attributed to the azole class of antifungal agents.

- **Treatments**

Two posaconazole formulations were administered, within 3 dose cohorts. Treatment allocation will be stratified according to the following factors: Age Group 1 (Young Children: 2 years to < 7 years of age) and Age Group 2 (Older Children/Adolescents: 7 years to 17 years of age).

		POS IV Solution Treatment Period (minimum 10 days)		POS PFS Oral Treatment Period (minimum 10 days)
		Day 1	Day 2 through end of IV dosing	
Age Group 1 Young Children (2 to < 7 years old)	Dose Cohort # 1	3.5 mg/kg BID POS IV solution[a]	3.5 mg/kg once daily POS IV solution[a]	3.5 mg/kg once daily POS PFS[a]
	Dose Cohort # 2	4.5 mg/kg BID POS IV solution[a]	4.5 mg/kg once daily POS IV solution[a]	4.5 mg/kg once daily POS PFS[a]
	Dose Cohort # 3	6 mg/kg BID POS IV solution[a]	6 mg/kg once daily POS IV solution[a]	6 mg/kg once daily POS PFS[a]
Age Group 2 Adolescents/Older Children (7 to 17 years old)	Dose Cohort # 1	3.5 mg/kg BID POS IV solution[a]	3.5 mg/kg once daily POS IV solution[a]	3.5 mg/kg once daily POS PFS[a]
	Dose Cohort # 2	4.5 mg/kg BID POS IV solution[a]	4.5 mg/kg once daily POS IV solution[a]	4.5 mg/kg once daily POS PFS[a]
	Dose Cohort # 3	6 mg/kg BID POS IV solution[a]	6 mg/kg once daily POS IV solution[a]	6 mg/kg once daily POS PFS[a]

[a] Maximum dose of 300 mg per administration

- Young children (Age Group 1, ages 2 to <7 years) and adolescents/older children Age Group 2, (ages 7-17 years) will be enrolling in parallel.
- The duration of POS IV solution treatment may be extended beyond 10 days if subjects are unwilling or unable to transition to POS PFS.
- The combined duration of POS treatment, either as POS IV solution or POS PFS, for each subject cannot exceed 28 days.
- Safety and PK data will be assessed separately for each dose cohort in 2 age groups.

All doses of POS IV solution will be based on the subject's age and the actual body weight as measured on Day 1, and will remain the same for all subsequent IV doses (through Day 10, or beyond Day 10, for subjects unable or unwilling to transition to POS PFS). Similarly, all doses of POS PFS will be based on the subject's age and the actual body weight as measured on the first day of oral treatment, and will remain the same for all subsequent oral doses. There is no dose escalation for individual subjects.

Patients receiving other systemic (PO or IV) antifungal agents as prophylactic therapy must discontinue those treatments prior to study drug administration. No other systemic anti-fungal agents may be administered during the POS treatment phase without Sponsor approval.

- **Objectives**

Primary objective: To evaluate the pharmacokinetics (PK) of POS IV solution and POS PFS administered to immunocompromised paediatric subjects (ages 2 years to 17 years) with neutropenia or expected neutropenia.

Secondary and exploratory objectives: To evaluate the safety and tolerability of POS IV solution and POS PFS administered to immunocompromised paediatric subjects (ages 2 years to 17 years) with neutropenia or expected neutropenia; to evaluate the palatability and acceptability of POS PFS; to evaluate the PK of sulfobutylether-beta-cyclodextrin (SBEβCD).

- **Outcomes/endpoints**

The primary endpoint is Cavg for both the POS IV solution and POS OGS. The Cavg is calculated by dividing the AUC with dosing interval. Additionally, Cmin, Cmax, Tmax, and AUC are also calculated for patients in each age group per dose cohort.

Safety is assessed based on adverse events, physical examinations, vital signs, clinical laboratory test results, and electrocardiogram (ECG) results. All subjects who receive at least one dose of study treatment are included in the safety analysis.

Palatability and acceptability parameters for the new POS OGS formulation are assessed in all subjects.

In addition, the PK of sulfobutylether-beta-cyclodextrin (SBEβCD) is also assessed as an exploratory objective while on POS IV solution.

There is no efficacy endpoint.

- **Randomisation and Blinding (masking)**

This was a non-randomized open-label study.

- **Statistical methods**

A total of 70 subjects will be screened to obtain a minimum of 48 PK-evaluable subjects in the PK analysis. Only subjects who receive at least 7 days of POS IV solution therapy and complete the full POS PK sampling while on POS IV solution will be included in the non-compartmental PK analysis for the primary patient population.

All subjects who receive at least one dose of study drug will be included in the safety analysis.

There are no efficacy analyses planned for this study.

The CHMP considered that the design of this study was endorsed within the posaconazole PIP, and is consistent with those of PK bridge studies.

However, considering this design, the small number of patients and the prophylaxis indication of posaconazole in this study, a significant efficacy objective and endpoint cannot be defined. Nevertheless, as a surrogate marker of efficacy, the occurrence of IFI and survival status at Day 100 are analysed.

Results

- **Participant flow**

A total of 126 subjects were screened of which 118 were enrolled in the study. Eight subjects were screened and did not meet inclusion criteria or did meet exclusion criteria.

Of the 118 subjects enrolled, 115 subjects were dosed, 2 subjects were deemed as screen failures after enrolment, and one subject's parent/guardian withdrew consent.

Of the 118 enrolled subjects, 109 (92.4%) completed the study. The number/proportion of subjects who withdrew from the study were generally similar across dose cohorts in both age groups.

Of the 115 subjects dosed with POS IV, 89 (77.4%) completed treatment. Of the 63 subjects who transitioned to POS PFS, 52 (82.5%) completed treatment.

	Treatment 3.5 mg/kg: Age Group 1 (2-<7 years old)		Treatment 3.5 mg/kg: Age Group 2 (7-17 years old)		Treatment 4.5 mg/kg: Age Group 1 (2-<7 years old)		Treatment 4.5 mg/kg: Age Group 2 (7-17 years old)	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	16		21		15		17	
Status for Trial†								
Completed	14	(87.5)	20	(95.2)	14	(93.3)	16	(94.1)
Discontinued	2	(12.5)	1	(4.8)	1	(6.7)	1	(5.9)
Adverse Event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Death	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Physician Decision	0	(0.0)	1	(4.8)	1	(6.7)	0	(0.0)
Protocol Deviation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Screen Failure	1	(6.3)	0	(0.0)	0	(0.0)	1	(5.9)
Withdrawal By Parent/Guardian	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)
Status for Study Medication in Trial Segment Intravenous (IV) Treatment††								
Started	14		21		15		16	
Completed	9	(64.3)	15	(71.4)	15	(100.0)	12	(75.0)
Discontinued	5	(35.7)	6	(28.6)	0	(0.0)	4	(25.0)
Adverse Event	3	(21.4)	3	(14.3)	0	(0.0)	2	(12.5)
Physician Decision	2	(14.3)	2	(9.5)	0	(0.0)	2	(12.5)
Protocol Deviation	0	(0.0)	1	(4.8)	0	(0.0)	0	(0.0)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Status for Study Medication in Trial Segment Oral (PFS) Treatment††								
Started	6		11		9		9	
Completed	5	(83.3)	10	(90.9)	8	(88.9)	9	(100.0)
Discontinued	1	(16.7)	1	(9.1)	1	(11.1)	0	(0.0)
Adverse Event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Physician Decision	0	(0.0)	0	(0.0)	1	(11.1)	0	(0.0)

	Treatment 6 mg/kg: Age Group 1 (2-<7 years old)		Treatment 6 mg/kg: Age Group 2 (7-17 years old)		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	20		29		118	
Status for Trial†						
Completed	19	(95.0)	26	(89.7)	109	(92.4)
Discontinued	1	(5.0)	3	(10.3)	9	(7.6)
Adverse Event	0	(0.0)	1	(3.4)	1	(0.8)
Death	1	(5.0)	1	(3.4)	2	(1.7)
Physician Decision	0	(0.0)	0	(0.0)	2	(1.7)
Protocol Deviation	0	(0.0)	1	(3.4)	1	(0.8)
Screen Failure	0	(0.0)	0	(0.0)	2	(1.7)
Withdrawal By Parent/Guardian	0	(0.0)	0	(0.0)	1	(0.8)
Status for Study Medication in Trial Segment Intravenous (IV) Treatment††						
Started	20		29		115	
Completed	18	(90.0)	20	(69.0)	89	(77.4)
Discontinued	2	(10.0)	9	(31.0)	26	(22.6)
Adverse Event	1	(5.0)	5	(17.2)	14	(12.2)
Physician Decision	0	(0.0)	4	(13.8)	10	(8.7)
Protocol Deviation	0	(0.0)	0	(0.0)	1	(0.9)
Withdrawal By Parent/Guardian	1	(5.0)	0	(0.0)	1	(0.9)
Status for Study Medication in Trial Segment Oral (PFS) Treatment††						
Started	14		14		63	
Completed	7	(50.0)	13	(92.9)	52	(82.5)
Discontinued	7	(50.0)	1	(7.1)	11	(17.5)
Adverse Event	3	(21.4)	1	(7.1)	4	(6.3)
Physician Decision	3	(21.4)	0	(0.0)	4	(6.3)

† Percentages are based on the number of all enrolled subjects.
†† Percentages are based on the number of subjects who started that treatment period.

The CHMP noted that the level of screen failure (6%) and study discontinuation (7.6%) are low for such paediatric population. However, the rates of treatment discontinuations are significant: 22.6% of subjects have discontinued from POS IV treatment, and 17.5% of subjects who have start the POS PFS formulation have discontinued. These treatments discontinuations were mainly due to adverse events and physician decision. Furthermore, the rate of treatment discontinuation for POS PFS in the younger subjects (Age Group 1) was higher in the 6 mg/kg cohort (7/14, 50%) than in the other age/dose cohorts (0% to 16.7%). Nevertheless, the number of subjects was too low to draw any conclusion from these discontinuation figures.

- **Conduct of the study**

A total of 29 sites were open for enrolment, of which 24 centers in 11 countries enrolled at least one subject.

Important deviations (i.e. those that may significantly impact the quality or integrity of key trial data or that may significantly affect a subject's rights, safety, or well-being) were reported for 45 subjects

(39.1%). Overall, 12 subjects had important protocol deviations related to study intervention, 10 of which affected POS IV dosing and 2 of which affected POS PFS dosing. Subjects with deviations affecting study intervention were only excluded from PK analyses if based on the timing and nature of the deviation the subject did not satisfy prespecified Patient Acceptability Criteria. Subjects whose data were excluded from analyses. No important protocol deviations were classified as GCP compliance issues.

	Treatment 3.5 mg/kg		Treatment 4.5 mg/kg		Treatment 6 mg/kg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	35		31		49		115	
With one or more important protocol deviations	13	(37.1)	7	(22.6)	25	(51.0)	45	(39.1)
With no important protocol deviations	22	(62.9)	24	(77.4)	24	(49.0)	70	(60.9)
Discontinuation Criteria	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(2.0)**	**1**	**(0.9)**
Subjects who developed withdrawal criteria but were not withdrawn	0	(0.0)	0	(0.0)	1	(2.0)	1	(0.9)
Inclusion/ Exclusion Criteria	**4**	**(11.4)**	**0**	**(0.0)**	**0**	**(0.0)**	**4**	**(3.5)**
Participants entered into the trial, i.e. progressed beyond screening, who did not meet key inclusion/exclusion criteria	3	(8.6)	0	(0.0)	0	(0.0)	3	(2.6)
Subject does not have appropriate qualifying clinical diagnosis (parameters defined per protocol)	1	(2.9)	0	(0.0)	0	(0.0)	1	(0.9)
Informed Consent Form	**1**	**(2.9)**	**2**	**(6.5)**	**3**	**(6.1)**	**6**	**(5.2)**
Participants with no documented initial consent to enter the trial.	1	(2.9)	2	(6.5)	3	(6.1)	6	(5.2)
Prohibited Medications	**2**	**(5.7)**	**0**	**(0.0)**	**2**	**(4.1)**	**4**	**(3.5)**
Prohibited Medications	2	(5.7)	0	(0.0)	2	(4.1)	4	(3.5)
Safety Reporting	**2**	**(5.7)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(1.7)**
Participants with reportable Safety Events and/or follow up Safety Event information that were not reported per the timelines outlined in the protocol.	2	(5.7)	0	(0.0)	0	(0.0)	2	(1.7)
Study Intervention	**3**	**(8.6)**	**2**	**(6.5)**	**7**	**(14.3)**	**12**	**(10.4)**
Subjects who received incorrect study treatment	3	(8.6)	2	(6.5)	7	(14.3)	12	(10.4)

Compliance with the study intervention regimen was high across the intervention groups, with the majority of subjects being >90% compliant (112 subjects [97.4%]) for POS IV treatment and >90% compliant (62 subjects [98.4%]) for POS PFS treatment.

- **Baseline data**

	Treatment 3.5 mg/kg Age Group 1 (2-<7 years old) n (%)	Treatment 3.5 mg/kg Age Group 2 (7-17 years old) n (%)	Treatment 4.5 mg/kg Age Group 1 (2-<7 years old) n (%)	Treatment 4.5 mg/kg Age Group 2 (7-17 years old) n (%)	Treatment 6 mg/kg Age Group 1 (2-<7 years old) n (%)	Treatment 6 mg/kg Age Group 2 (7-17 years old) n (%)	Total n (%)
Subjects in Population†	14	21	15	16	20	29	115
Gender							
Male	12 (85.7)	10 (47.6)	7 (46.7)	9 (56.3)	10 (50.0)	19 (65.5)	67 (58.3)
Female	2 (14.3)	11 (52.4)	8 (53.3)	7 (43.8)	10 (50.0)	10 (34.5)	48 (41.7)
Age (Years)							
Mean	3.93	13.86	4.07	12.19	3.85	12.00	8.93
SD	1.44	2.08	1.44	2.48	1.60	3.47	4.95
Median	3.00	14.00	4.00	12.00	3.50	12.00	8.00
Range	2 to 6	10 to 17	2 to 6	7 to 16	2 to 7	7 to 17	2 to 17
Race							
Asian	4 (28.6)	1 (4.8)	2 (13.3)	2 (12.5)	1 (5.0)	1 (3.4)	11 (9.6)
Black Or African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	2 (6.9)	3 (2.6)
Multiple	0 (0.0)	2 (9.5)	0 (0.0)	2 (12.5)	0 (0.0)	0 (0.0)	4 (3.5)
Native Hawaiian Or Other Pacific Islander	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
White	10 (71.4)	18 (85.7)	12 (80.0)	12 (75.0)	18 (90.0)	26 (89.7)	96 (83.5)
Ethnicity							
Hispanic Or Latino	1 (7.1)	2 (9.5)	2 (13.3)	4 (25.0)	1 (5.0)	2 (6.9)	12 (10.4)
Not Hispanic or Latino	13 (92.9)	19 (90.5)	12 (80.0)	11 (68.8)	18 (90.0)	27 (93.1)	100 (87.0)
Not Reported/Unknown	0 (0.0)	0 (0.0)	1 (6.7)	1 (6.3)	1 (5.0)	0 (0.0)	3 (2.6)
Specific Baseline Disease††							
Acute Leukemia	3 (21.4)	8 (38.1)	4 (26.7)	11 (68.8)	8 (40.0)	17 (58.6)	51 (44.3)
Myelodysplasia	0 (0.0)	0 (0.0)	1 (6.7)	1 (6.3)	0 (0.0)	2 (6.9)	4 (3.5)
Severe Aplastic Anemia	3 (21.4)	3 (14.3)	3 (20.0)	1 (6.3)	2 (10.0)	1 (3.4)	13 (11.3)
Recipients of HSCT	7 (50.0)	13 (61.9)	9 (60.0)	2 (12.5)	7 (35.0)	13 (44.8)	51 (44.3)
High Risk Neuroblastoma	2 (14.3)	0 (0.0)	5 (33.3)	2 (12.5)	5 (25.0)	2 (6.9)	16 (13.9)
Advanced stage NHL	0 (0.0)	1 (4.8)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	2 (1.7)
Hemophagocytic Lymphohistiocytosis	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	2 (1.7)
Other‡	0 (0.0)	1 (4.8)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)
Weight (kg)							
Mean	18.61	53.40	17.42	49.02	17.43	46.25	35.80
SD	7.26	14.72	3.69	21.11	5.12	23.16	22.13
Median	15.85	51.50	17.60	44.20	16.40	39.30	28.60

Range	12.8 to 41.7	24.7 to 83.3	12.3 to 24.4	21.3 to 95.8	10.2 to 28.6	18.2 to 101.6	10.2 to 101.6
Height (cm)							
Mean	103.82	160.62	105.81	153.39	104.20	153.22	133.97
SD	11.68	14.36	11.50	15.98	13.86	23.54	30.34
Median	100.00	160.00	109.00	156.00	102.00	150.00	132.00
Range	87 to 122.5	133 to 189.6	81.6 to 119	125 to 182	83 to 130	114 to 195	81.6 to 195

† 3 subjects were enrolled but not treated.

†† It is possible for a subject to have more than one condition. Subjects with multiple conditions will be counted once in each condition. Subjects who do not have any of these 7 specific diseases reported will be counted in Other category.

‡ Baseline disease for the 2 subjects categorized as Other were alveolar rhabdomyosarcoma, and receipt of an autologous bone marrow transplantation.

HSCT=hematopoietic stem cell transplantation, NHL=non-Hodgkin's lymphoma.

Weight and height are summarized using the last observation prior to the first dose of study drug.

The majority of subjects were white (83.5%) and male (58.3%). The most common underlying conditions that qualified subjects for enrolment were acute leukemia (44.3%), HSCT (44.3%), and high-risk neuroblastoma (13.9%). Younger subjects were more likely to have a medical diagnosis of neuroblastoma or aplastic anemia, and less likely to have a medical diagnosis of leukemia.

The CHMP noted that large weights (from 10 to 101 kg, with a median at 28.6 kg) and ages (from 2 to 17 years old, including 49 subjects <7 years old) categories were included, supporting the reliability of the PK assessment for such population.

Nevertheless, baseline race and ethnicity are not well diversified, with notably a low proportion of African subjects (2.6%). Of note, based on Noxafil SmPC, there was a slight decrease (16 %) in the AUC and C_{max} of posaconazole oral suspension in Black subjects relative to Caucasian subjects, but with similar safety profile. However, the population pharmacokinetic analysis suggests that ethnicity have no clinically meaningful effect on the pharmacokinetics of posaconazole.

- **Numbers analysed**

The PK analysis population included a total of 100 subjects for the IV treatment and 50 subjects for the PFS treatment for the primary endpoint. Of the 115 subjects started on IV treatment, 15 (13%) did not meet Patient Acceptability Criteria and were not included in PK analysis. Reasons for exclusion included the following: samples were not collected, or PK concentrations not obtained 9/15 (60%), dose was not given within 6 hours of the scheduled time 5/15 (33.3%), and outlier exclusion 1/15 (6.7%). Sixty-three subjects successfully transitioned to the PFS treatment and received at least one dose. Of these, 13 (20.6%) did not meet Patient Acceptability Criteria and were not included in PK analysis. Reasons for exclusion included the following: PK concentrations or samples were not collected 10/13 (76.9%), and incomplete dose taken 3/13 (23.1%).

Dose Cohort	Age Group	Dose Type	Patients that received study drug	Patients Included in PK analysis
3.5 mg/kg	1 (2 to <7 yrs old)	IV	14	11
		PFS	6	5
	2 (7 to 17 yrs old)	IV	21	19
		PFS	11	10
4.5 mg/kg	1 (2 to <7 yrs old)	IV	15	14
		PFS	9	8
	2 (7 to 17 yrs old)	IV	16	15
		PFS	9	8
6.0 mg/kg	1 (2 to <7 yrs old)	IV	20	17
		PFS	14	7
	2 (7 to 17 yrs old)	IV	29	24
		PFS	14	12

Safety analyses were based on all 115 enrolled subjects who received at least one dose of study intervention.

- **Outcomes and estimation**

P097 was not designed as an efficacy study; however, efficacy data, ie, the occurrence of AEs consistent with IFI and Day 100 survival, were collected for the 115 subjects who were enrolled and received study therapy.

Occurrence of IFI

Two of 115 posaconazole-treated paediatric subjects (1.7%) experienced AEs consistent with IFI. Both subjects were in the 4.5 mg/kg/day dose cohort:

- One subject experienced an AE of systemic mycosis, with onset on Day 11 as fever of unknown origin with computed tomography scan showing evidence of splenic and lung lesions possibly consistent with a fungal etiology. POS IV had been discontinued on Day 7 due to an AE of pyrexia with the investigator decision to start therapy with amphotericin B.

- One subject had an AE of fungal infection with onset on Day 7 as fever and skin nodules. POS IV was discontinued, and the subject was started on amphotericin B.

Both of these subjects had IV POS Cavg concentrations within the target therapeutic range (subject 1, 1190 ng/ml; and subject 2, 1180 ng/mL), which were comparable to the mean Cavg for this dose/age group (mean Cavg 1240 ng/mL). Both AEs were considered resolved by the end of study follow up.

No AEs consistent with IFI were reported in the 3.5 mg/kg/day or 6 mg/kg/day dose cohorts.

The CHMP acknowledged that, as stated by the MAH, the rate of AEs consistent with IFI is comparable to those observed in prior prophylaxis studies with the tablet or OS formulation:

- In a study of neutropenic adult patients receiving the posaconazole tablet (P05615), 1 of 210 subjects (<1%) treated with the 300 mg daily dose was diagnosed with an IFI.

- In one of the pivotal Phase 3 studies of the OS formulation (C/I98-316) in adult allogeneic HSCT recipients with acute or chronic GVHD, 5% of subjects (16/301) in the posaconazole group experienced

an IFI at exposures equivalent to those expected in paediatric patients at a dose of 6 mg/kg/day with IV or PFS.

- In the second pivotal study of the posaconazole OS formulation (P01899), in adults with prolonged neutropenia after cytotoxic chemotherapy for the induction of remission in primary or relapsed acute myelogenous leukemia or myelodysplastic syndrome, 7/304 subjects (2%) experienced an IFI at exposures equivalent to those expected in paediatric patients at a dose of 6 mg/kg/day with IV or PFS.

Furthermore, the two cases of IFI occurring in study P097 were not associated to suboptimal posaconazole exposure.

Day 100 survival status

P097: Day 100 Survival Status
All Treated Subjects

	Treatment 3.5 mg/kg Age Group 1 (2-<7 years old) n (%)	Treatment 3.5 mg/kg Age Group 2 (7-17 years old) n (%)	Treatment 4.5 mg/kg Age Group 1 (2-<7 years old) n (%)	Treatment 4.5 mg/kg Age Group 2 (7-17 years old) n (%)	Treatment 6 mg/kg Age Group 1 (2-<7 years old) n (%)	Treatment 6 mg/kg Age Group 2 (7-17 years old) n (%)	Total n (%)
Subjects in Population	14	21	15	16	20	29	115
Status for Trial							
Alive	13 (92.9)	21 (100.0)	15 (100.0)	16 (100.0)	19 (95.0)	27 (93.1)	111 (96.5)
Death	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	2 (6.9)	4 (3.5)
Lost to follow up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No Contact Made	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject Withdrew Consent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The CHMP noted that, according to the MAH, the survival data for posaconazole IV and PFS formulations were comparable to the corresponding data previously reported from clinical trials of the posaconazole tablet and OS formulations for antifungal prophylaxis in adults (P05615: Day 65 survival rate at 91%; P01899: Day 65 survival rate at 87%; C/I98-316: Day 65 survival rate at 86%).

- **Ancillary analyses**

No relevant subgroup analyses were performed.

Palatability and acceptability parameters for the POS PFS formulation were assessed by questionnaire on Day 1 and Day 3-5 of POS PFS therapy and at the EOT visit.

The majority of palatability assessment questionnaires were completed by a nurse or primary caregiver for Age Group 1 and by the subject for Age Group 2. Taste was assessed as "average," "good," or "very good" by the majority of assessors for both age groups and all doses at all time points. The majority of subjects in both age groups and all doses at all time points did not report any problems taking the PFS dose. Problems reported by a minority of subjects included refusing or spitting out the dose, vomiting or spitting up, and gagging. The majority of subjects administered the POS PFS formulation found the oral formulation to be palatable and acceptable.

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

The MAH performed a literature research on the post-marketing use of posaconazole OS, tablet, and IV formulations in paediatric patients since 2005.

More than 100 studies and case reports have been published in the medical literature. Most of these publications describe the safe and effective use of posaconazole (OS, tablet and OV formulation) for the prevention and treatment of IFI in paediatric patients. Several of these reports have included plasma posaconazole levels, as well as preliminary efficacy data, and are described below:

- Doring et al. (2017) reported on the efficacy and safety of posaconazole tablet or OS given as antifungal prophylaxis to children following HSCT at a single center, with posaconazole plasma levels measured. The study used a weight-based dosing regimen to provide posaconazole 100-mg tablets divided into 50-mg increments (from 100 to 300 mg). Thirty-two subjects (median age 14 years, range 3-17 years) received posaconazole tablet at dosages ranging from 5 to 7 mg/kg/day (BID on Day 1). After 14 days of therapy, 31 of 32 (96.8%) subjects had trough concentrations ≥500 ng/mL. The median treatment period was 91 days. During a median observation period of 106 days, there were no reports of proven, probable or possible IFI or deaths; furthermore, galactomannan values were normal among all subjects.

- A recent retrospective study by Mauro et al (2020) of posaconazole tablet enrolled 28 hematology/oncology patients at 6 sites in Italy (median age 15 years, range 5-18 years) who had undergone chemotherapy or HSCT and received posaconazole as either prophylaxis (21 patients) or treatment (7 patients) of IFI. Patients with a body weight of <50 kg received posaconazole tablet at 4 to 6 mg/kg/day as a starting dose, with adjustments made on the basis of measured plasma concentration. Among the 13 patients who received posaconazole tablet as prophylaxis, with a median dosage of 5 to 6 mg/kg/day, median plasma concentrations at 7, 14, and 28 days after beginning treatment were 1300 to 1400 ng/mL, with a broad concentration range, primarily at the latter time points. None of these patients had evidence of IFI during prophylaxis. Among the 7 patients who received posaconazole tablet as therapy (2 patients) or salvage therapy (5 patients), starting a median of 21 days (range 7-204 days) after symptoms began, with a median dosage of 4 mg/kg/day, median plasma concentrations at 7, 14, and 28 days were 900 to 2700 ng/mL. Response outcomes were available for 6 of these patients: 4 had a complete or partial response, 1 had a stable response, and 1 had worsened status.

- Another recent retrospective study of posaconazole tablet among paediatric patients by Tragiannidis et al (2019), at a single paediatric oncology hospital in Germany, enrolled 34 patients (median age 12 years, range 5-17 years) who were prescribed posaconazole tablet as primary or secondary prophylaxis; of these, 11 patients had had allogeneic HSCT, and 1 patient had polyarthritis, all of whom were receiving immunosuppressive therapy. Weight-dependent dosages were 300 mg QD (BID on Day 1) in 25 patients with body weight >30 kg, and alternating doses of 200 and 300 mg QD (300 mg on Day 1) in 9 patients with body weight >20-30 kg. Dosages were subsequently increased or decreased in a total of 5 patients in both groups in order to maintain a trough concentration of ≥1000 ng/mL and ≤5000 ng/mL. Approximately 90% of both children (aged 5 through 12 years) and adolescents (aged 13 through 17 years) had posaconazole trough concentrations ≥700 ng/mL. Over a median duration of 70 days of prophylaxis treatment (range 9-391 days), no IFI was observed among the 34 patients.

- A recent publication by Nickless et al (2018) reported on the use of posaconazole IV at a single paediatric hospital between 2015 and 2017. Eligible children for this review weighed <40 kg, received ≥5 doses of posaconazole IV and had ≥1 posaconazole level measured. Children were prescribed posaconazole IV if they could not tolerate posaconazole OS or were not able to take any oral therapy. The review identified 10 subjects from 1.5 through 11 years of age who received posaconazole IV for

either treatment or prevention of an IFI. In this study, therapeutic drug monitoring of posaconazole levels was performed and the once-daily dose of posaconazole IV adjusted to maintain a minimum desired target. It was found that, in this patient population, posaconazole IV at doses of 5.3 to 13.5 mg/kg/day (with a median minimum effective dose of 6.55 mg/kg/day) was generally successful in achieving a trough concentration of >700 ng/mL.

The posaconazole exposures achieved in these studies have been associated with efficacy in adult studies of the OS formulation. Collectively, the results described above support the efficacy of posaconazole in children and adolescents (2 to <18 years of age).

Currently, only voriconazole is indicated for the prophylaxis of IFI in children. Considering its side effects and drug-drug interaction profile, there is an off-label use of posaconazole in immunocompromised children. This literature research highlights the need to extend the indication of posaconazole for prophylaxis and treatment of IFI in paediatric subjects. The CHMP considered that these data support the efficacy of posaconazole for the treatment or prophylaxis of IFI.

2.6.6. Discussion on clinical efficacy

Prior to this extension of indication, Posaconazole was indicated in the treatment and prophylaxis of the following IFI 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); oropharyngeal candidiasis (as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor).

The available antifungals approved in paediatric subjects at the time of this Assessment Report are: amphotericin B, caspofungin, micafungin, flucytosine, fluconazole and voriconazole. Only mycafungin (for candidemia), fluconazole (for candidemia and cryptococcosis) and voriconazole (for candidemia, aspergillosis and fusariosis) have a prophylaxis indication in immunocompromised children. The choice of antifungal prophylaxis for paediatric patients is limited by side effects profiles, drug-drug interactions, PK characteristics, antifungal spectrum and also availability of oral formulation for young children. Therefore, there is a medical need to extend the indication of posaconazole to paediatric subjects.

This paediatric extension of posaconazole was discussed and approved within its PIP. Given no dose could be defined with the available oral solution (based on PK results of study P032), a new oral formulation (powder for oral solution) was developed and paediatric doses were defined within the study P097.

Design and conduct of clinical studies

This paediatric extension of indication is based on the PK bridge study P097 performed in immunocompromised children. This PK approach to define a paediatric posology and the design of this sequential dose-escalation study, assessing 3 doses of posaconazole (3.5, 4.5 and 6 mg/kg/day), were approved by the EMA Paediatric Committee.

This study was not design for efficacy assessment (all the more that posaconazole was administered in

a prophylaxis indication, for which an efficacy assessment requires a large population), and a significant efficacy objective and endpoint cannot be defined. Nevertheless, as a surrogate marker of efficacy, the occurrence of IFI and survival status at Day 100 were analysed.

Efficacy data and additional analyses

Overall, 115 subjects were included in the study, with large weights range (from 10 to 101 kg, with a median at 28.6 kg) and ages range (from 2 to 17 years old, including 49 subjects <7 years old), supporting the reliability of the PK assessment for such population. The majority of subjects were male (58.3% of male subjects) with immunocompromised status associated with acute leukemia (44.3%), HSCT (44.3%), or high-risk neuroblastoma (13.9%). The included population may be considered representative, although baseline race and ethnicity are not well diversified, with notably a low proportion of African subjects (2.6%). Of note, based on Noxafil SmPC, there was a slight decrease (16 %) in the AUC and C_{max} of posaconazole oral suspension in Black subjects relative to Caucasian subjects, but with similar safety profile. However, the population pharmacokinetic analysis suggests that ethnicity have no clinically meaningful effect on the pharmacokinetics of posaconazole.

The occurrence of IFI (2/115 subjects, 1.7%) is comparable to those observed in prior prophylaxis studies with the tablet or OS formulation in adults (1-2%). Similarly, the survival status (at Day 100: 111/115 subjects, 96.5%) is comparable to those previously reported in clinical trials with the tablet and OS formulations for antifungal prophylaxis in adults (at Day 65: 86-91%). Furthermore, based on literature data, the efficacy of posaconazole in paediatric population was assessed and supported within several clinical studies.

Importantly a paediatric formulation, the taste of the new oral formulation (powder for solution) seems to be well accepted by this paediatric population, with a high compliance within this study (98.4% for PFS treatment).

2.6.7. Conclusions on the clinical efficacy

No new efficacy conclusion can be drawn with this paediatric PK bridge study. However, no efficacy concerns were highlighted among the 115 paediatric subjects (including 49 subjects treated with the recommended dose at 6 mg/kg), which is reassuring as regards the predicted and non-negligible percentage of paediatric subjects from 2 to <7 years old (6.8%) to have a Cavg below the target of 500 ng/mL (see PK discussion).

Considering that Noxafil (and posaconazole generics) are currently available as oral suspension, it is considered important to differentiate them from the new PFS formulation of Noxafil. Indeed, no paediatric dose could be defined with posaconazole oral solution throughout the study P032, as the PK exposure target was not met with any dose of this OS formulation. The co-marketing of two oral solutions may be confusing and potentially lead to dosing error. As Noxafil PFS was not developed for adults, it is important to well characterise the current Noxafil oral solution for adults only, and the new Noxafil PFS for paediatric subjects only. This is addressed *via* a one-time DHPC to inform on the availability and indication of the two formulations.

2.6.8. Clinical safety

The posaconazole (POS; Noxafil®; MK-5592) paediatric clinical development program is ongoing to evaluate the use of posaconazole in paediatric patients 2 years of age and older. The proposed indications

are supported by a PK and safety bridging strategy to currently approved indications in adults, which may differ by country/region.

The IV formulation of posaconazole (concentrate for solution for infusion) investigated in P097 is identical to that commercially available and approved for use in adults. A novel powder for oral suspension (PFS), also referred to as a powder for delayed-release oral suspension or gastro-resistant powder for oral suspension, referred to hereafter as PFS, has been developed to offer the improved bioavailability of the posaconazole delayed-release tablet in a formulation that is amenable for oral administration in younger children and for weight-based dosing.

In addition to P097, the PK and safety of posaconazole in paediatric patients have also been studied in P032 (P03579), the first clinical study designed to identify a paediatric dose for posaconazole using the oral suspension (OS) formulation approved for use in adults. P032 was a Phase 1b, nonrandomized, multicenter, open-label, sequential dose-escalation study of the PK, safety, and tolerability of posaconazole OS when used as prophylaxis in immunocompromised paediatric subjects (3 months to <18 years of age) who were at high risk for invasive fungal infections (IFIs). The study was terminated early based on analysis of PK data demonstrating that the PK exposure target for the study was not met with any of the doses studied.

Posaconazole OS was generally well tolerated in paediatric subjects age 2 to <18 years at all administered doses (12 mg/kg/day divided BID, 18 mg/kg/day divided BID and 18 mg/kg/day divided TID) in the P032 study. There was no apparent pattern to suggest a difference in the safety profiles among the three dosing schedules evaluated, nor between the younger (2 to <7 year old) and older age (7 to <18 years of age) groups.

2.6.8.1. Patient exposure

Of the 115 subjects (P097) treated with posaconazole IV, 89 (77.4%) completed treatment. Of the 63 subjects who transitioned to posaconazole PFS, 52 (82.5%) completed treatment.

The mean overall treatment duration (posaconazole IV and posaconazole PFS) of all treated subjects was 20.6 days with a range of 1 to 28 days. The mean duration of posaconazole IV treatment was 14.3 days (range, 1 to 28 days), and the mean duration of posaconazole PFS treatment was 11.6 days (range, 2 to 18 days).

Although there were differences in baseline characteristics between some groups, no clinically meaningful differences were observed between the groups.

The most common underlying conditions that qualified subjects for enrolment were acute leukemia, HSCT, and high-risk neuroblastoma. Younger subjects were more likely to have a medical diagnosis of neuroblastoma or aplastic anemia, and less likely to have a medical diagnosis of leukemia.

Across the two studies, 250 paediatric subjects aged 2 to < 18 years of age and 1 subject under 1 year of age were exposed to posaconazole for up to 28 days.

The CHMP noted that, across the two studies (P032 and P097), 250 paediatric subjects aged 2 to < 18 years of age and 1 subject under 1 year of age were exposed to posaconazole.

In P097, 115 subjects were treated with posaconazole IV. Among them, 63 subjects transitioned with posaconazole PFS.

2.6.8.2. Adverse events

- P032 and P097

Overall rates of AEs, including rates of SAEs, deaths, and discontinuations due to AEs, were generally comparable between the age groups for both P097 and P032. Therefore, the two age groups are combined in subsequent data presentations in the remainder of the integrated analysis. Overall, a higher proportion of subjects enrolled in P032 reported, drug-related AEs and AEs leading to discontinuation of study medication than in P097. The rates of all other AE categories were similar between the two studies.

- P097

The frequencies of AEs across all AE categories were generally similar between dose cohorts and age group. Overall AE frequencies were lower during treatment with the PFS formulation than during the initial treatment with the IV formulation.

There was no pattern to AEs that would indicate a clear difference between the dose cohorts or age groups.

Reported AEs were generally consistent with those expected in a paediatric oncology population undergoing treatment for malignancy or with the known safety profile of posaconazole.

There was no pattern to drug-related AEs that would indicate a clear difference among the dose cohorts or age groups. Reported drug-related AEs were generally consistent with the known drug-related AEs of posaconazole in adults.

Table 22 Subjects with Drug-Related Adverse Events (Incidence ≥ 5% in One or More Treatment Groups by dose cohort – All Subjects as Treated (P097)

	Treatment 3.5 mg/kg		Treatment 4.5 mg/kg		Treatment 6 mg/kg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	35		31		49		115	
with one or more drug-related adverse events	4	(11.4)	8	(25.8)	5	(10.2)	17	(14.8)
with no drug-related adverse events	31	(88.6)	23	(74.2)	44	(89.8)	98	(85.2)
Gastrointestinal disorders	**0**	**(0.0)**	**2**	**(6.5)**	**0**	**(0.0)**	**2**	**(1.7)**
Hepatobiliary disorders	**0**	**(0.0)**	**2**	**(6.5)**	**0**	**(0.0)**	**2**	**(1.7)**
Hyperbilirubinaemia	0	(0.0)	2	(6.5)	0	(0.0)	2	(1.7)
Investigations	**3**	**(8.6)**	**3**	**(9.7)**	**2**	**(4.1)**	**8**	**(7.0)**
Aspartate aminotransferase increased	1	(2.9)	2	(6.5)	1	(2.0)	4	(3.5)
Drug level increased	2	(5.7)	0	(0.0)	0	(0.0)	2	(1.7)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**2**	**(6.5)**	**2**	**(4.1)**	**4**	**(3.5)**
Rash	0	(0.0)	2	(6.5)	1	(2.0)	3	(2.6)

Every subject is counted a single time for each applicable row and column.

A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Table 23 Adverse Event Summary by Age Group – All Subjects as Treated

	P097 Age 2<7 years		P097 Age 7 -17 years		P032 Age 2<7 years		P032 Age 7 -17 years		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	49		66		57		79		251	
with one or more adverse events	47	(95.9)	66	(100.0)	51	(89.5)	77	(97.5)	241	(96.0)
with no adverse event	2	(4.1)	0	(0.0)	6	(10.5)	2	(2.5)	10	(4.0)
with drug-related* adverse events	7	(14.3)	10	(15.2)	19	(33.3)	31	(39.2)	67	(26.7)
with serious adverse events	10	(20.4)	21	(31.8)	13	(22.8)	21	(26.6)	65	(25.9)
with serious drug-related adverse events	1	(2.0)	0	(0.0)	2	(3.5)	1	(1.3)	4	(1.6)
who died	0	(0.0)	2	(3.0)	1	(1.8)	2	(2.5)	5	(2.0)
who died to a drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued drug due to an adverse event	7	(14.3)	11	(16.7)	10	(17.5)	22	(27.8)	50	(19.9)
discontinued drug due to a drug-related adverse event	2	(4.1°	2	(3.0)	3	(5.3)	11	(13.9)	18	(7.2)
discontinued drug due to a serious adverse event	4	(8.2)	6	(9.1)	1	(1.8)	3	(3.8)	14	(5.6)
discontinued drug due to a serious drug-related adverse event	1	(2.0)	0	(0.0)	1	(1.8)	1	(1.3)	3	(1.2)

* Determined by the investigator to be related to the drug
Adverse events summary is based on treatment-emergent adverse events as defined in the respective protocols

The most common AEs (occurring in >20% of the pooled subjects) were pyrexia, vomiting, mucosal inflammation, febrile neutropenia, nausea, and diarrhea. Observed AEs were generally consistent with those expected in a paediatric oncology population undergoing treatment for malignancy, and with the established safety profile of posaconazole.

For the combined pool of subjects, 26.7% reported drug-related AEs. Common drug-related AEs (those occurring in ≥5% of subjects in the combined population) were nausea, vomiting, and ALT increased. It is noted that there were more drug-related adverse events in study P032 (oral suspension) compared to P097 (PFS), and that these differences appeared to be driven by a greater incidence of GI-related AE (nausea/vomiting) with the OS formulation.

The CHMP noted that no news AEs emerged in the paediatric population. Reported AEs were generally consistent with those expected in a paediatric oncology population undergoing treatment for malignancy or with the known safety profile of posaconazole. Adverse events incidence was high in all groups, which was expected in this critically ill population.

AE frequencies were lower during treatment with the PFS formulation than during the initial treatment with the IV formulation.

It is noted that there were more drug-related adverse events in study P032 (oral suspension) compared to P097 (PFS).

Most common reported AEs (occurring in >20% of subjects) were pyrexia, mucosal inflammation, vomiting, diarrhea and febrile neutropenia.

2.6.8.3. Serious adverse event/deaths/other significant events

- Deaths

Overall rates of deaths due to AEs were low in the combined population (2.0%) and in the individual studies (1.7% in P097, 2.2% in P032). No subject in either study died due to a drug-related AE.

In P097, a total of 4 subjects died after the end of study treatment, but before the final survival assessment (allowed range, Day 90 to 110). Three of the 4 subjects died before the Day 65 survival assessment. Two of these deaths occurred after the end of the AE monitoring period (through 14 days after last dose of study treatment) and were due to the subjects' underlying malignancy. Another 2 subjects died due to a fatal AE of respiratory failure and veno-occlusive disease, both of which occurred after the end of study treatment. None of the deaths was considered to be related to study treatment by the investigator.

The CHMP noted that 7 deaths were reported (4 in P097 and 3 in P032). None of the deaths was considered to be related to study treatment by the investigator.

- Serious Adverse Events

The overall incidence and distribution of SAEs were similar between age groups and dose cohorts. A total of 31 subjects (27.0%) experienced SAEs: 19 subjects during posaconazole IV treatment and 13 subjects during posaconazole PFS treatment. Reported serious AEs were generally consistent with those expected in a paediatric oncology population undergoing treatment for malignancy or with the safety profile of posaconazole established in adults.

Most SAEs were reported in <1% of the combined population with the exceptions of anemia (1.2%), pyrexia (1.6%), and febrile neutropenia (6.8%).

The CHMP noted that SAEs were reported in 27.0% of subjects. The most common SAE was febrile neutropenia (2.6%). Other SAEs occurring in >1% of subjects were veno-occlusive disease, pyrexia and vomiting. 4 experienced a drug-related AEs all resolved. These data were already analysed and validated as part of procedure EMEA/H/C/000610/P46/029.

- Treatment-Related Serious Adverse Events

The overall rate of drug-related SAEs (1.6%) was low in the combined pool and in the individual studies. This low rate is similar to overall rates of drug-related SAEs reported in adult studies (3% in P05615 with posaconazole tablet and 1% in P05520 with posaconazole IV formulation. Drug-related SAEs with an incidence ≥ 0% in one or more treatment groups are presented in Table 3. No individual drug-related SAE was reported in >1 subject in either treatment group

Table 24 – Subjects with serious drug-related adverse events (Incidence > 0% in One or More Treatment Groups)

	P097		P032		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	115		136		251	
with one or more serious drug-related adverse events	1	(0.9)	3	(2.2)	4	(1.6)
with no serious drug-related adverse events	114	(99.1)	133	(97.8)	247	(98.4)
Immune system disorders	**1**	**(0.9)**	**0**	**(0.0)**	**1**	**(0.4)**
Drug hypersensitivity	1	(0.9)	0	(0.0)	1	(0.4)
Investigations	**0**	**(0.0)**	**3**	**(2.2)**	**3**	**(1.2)**
Alanine aminotransferase increased	0	(0.0)	1	(0.7)	1	(0.4)
Aspartate aminotransferase increased	0	(0.0)	1	(0.7)	1	(0.4)
Chemotherapeutic drug level increased	0	(0.0)	1	(0.7)	1	(0.4)
Electrocardiogram T wave inversion	0	(0.0)	1	(0.7)	1	(0.4)
Transaminases increased	0	(0.0)	1	(0.7)	1	(0.4)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Adverse events were treatment-emergent adverse events as defined in the respective protocols.

Source: [ISS: adam-adsl; adae]

The CHMP noted that the overall rate of drug-related SAEs (1.6%) was low in the combined pool and in the individual studies. This low rate is similar to overall rates of drug-related SAEs reported in adult studies (3% in P05615 with posaconazole tablet and 1% in P05520 with posaconazole IV formulation. No individual drug-related SAE was reported in >1 subject in either treatment group.

- Medication errors

To ensure proper use of the newly introduced PFS formulation, the product labeling and package carton will clearly state that Noxafil OS and Noxafil PFS are not to be used interchangeably. Unlike Noxafil OS, which is a ready-to-use suspension, Noxafil PFS is provided as a powder that must be mixed with the suspending vehicle (also provided in the same product kit) before use. Notch-tip oral dosing syringes, a bottle of suspending vehicle, bottle adapter, mixing cups and a step-by-step Instruction for Use (IFU) are provided to guide the preparation and administration of weight-based dosing of the PFS. In addition, the Noxafil PFS kit and the additional syringe pack will be cross-labeled in the product labeling and the package cartons to ensure that the additional notch-tip syringes are supplied together with the PFS kit.

A new PFS formulation (Powder for oral suspension, also called "Gastro-Resistant Powder and Solvent for Oral Suspension) is introduced. However, as an oral suspension already exists (and is not interchangeable with the PFS), there may be a risk of confusion between these formulations leading to potential dosing errors, patients receiving incorrect formulation and/or dose of posaconazole, or either lack of efficacy (due to subtherapeutic drug levels) or drug toxicity (due to supratherapeutic drug levels). The MAH proposed a DHPC addressing the non-interchangeability between the oral suspension and the GR powder and solvent for oral suspension, which was acceptable to the CHMP.

In addition, the SmPC for the GR powder and solvent for oral suspension and respectively for the OS contain a statement of non-interchangeability.

2.6.8.4. Laboratory findings

- *Hematology and Chemistry Laboratory Values*

There was no pattern to laboratory toxicity grade changes that would indicate a clear difference between the dose cohorts or age groups.

None of the subjects had liver function laboratory findings that met predetermined criteria for potential drug-induced liver injury.

- *Vital signs*

There were variable increases in systolic and diastolic blood pressure from baseline across the dose cohorts that were not considered clinically meaningful. No subjects died or discontinued study treatment due to hypertension.

One subject in Age Group 2 of the 6 mg/kg Dose Cohort experienced an SAE of worsening hypertension that resolved and was reported by the investigator as not related to study treatment. There were no other clinically meaningful findings in vital sign measurements, physical examination assessments, or other observations related to safety in this study.

- *Electrocardiograms*

No subject in P097 met the protocol pre-specified criteria for prolonged QT (QTc ≥500 msec).

- *Exposure/Safety Analysis*

Despite a low incidence of drug-related AEs across dose cohorts, an exploratory analysis of drug-related AEs by steady-state Cavg concentrations for the posaconazole IV and posaconazole PFS formulations was performed. No correlation between drug-related AEs and posaconazole exposures was observed for either the posaconazole IV or posaconazole PFS formulations.

The CHMP noted that, considering the laboratory values, no signal was found.

2.6.8.5. Safety in special populations

Safety and Suitability of Posaconazole IV Formulation for Paediatric Patients.

The IV formulation of posaconazole is generally well tolerated and safe in adult and paediatric patients 2 years of age and above in clinical trials, as well as in postmarket use (including off-label in paediatric patients) since 2015.

Posaconazole IV formulation is an aqueous injectable solution containing 18 mg/mL of posaconazole to be diluted with sodium chloride 0.9% or 5% dextrose in water prior to IV administration. The primary excipient in posaconazole IV solution is sulfobutylether-β-cyclodextrin (SBEβCD, marketed as Captisol®), an excipient that is found in marketed IV products including voriconazole IV (VFEND®). SBEβCD has been associated with kidney toxicity in rat models. Also, SBEβCD is mainly excreted through the kidney; therefore, accumulation of SBEβCD is expected to occur when used in patients with moderate or severe renal impairment.

The final concentrations of posaconazole and SBEβCD are 18 mg/mL and 400 mg/mL, respectively. By comparison, the concentrations of voriconazole and SBEβCD are 10 mg/mL and 160 mg/mL, respectively. The overall exposure to SBEβCD in paediatric patients treated with posaconazole IV solution

is no greater than the exposure in those administered IV voriconazole. On a weight-normalized (mg/kg) basis, a daily maintenance dose of 6 mg/kg posaconazole IV QD would contain 133 mg/kg/day SBEβCD, whereas the approved daily maintenance dose of 8 mg/kg voriconazole IV BID would contain 256 mg/kg/day SBEβCD. The acceptable threshold for cyclodextrins (including SBEβCD) for parenteral route of administration greater than 2 weeks is 200 mg/kg/day per the Annex to the European Commission guideline on 'Excipients in the labeling and package leaflet of medicinal products for human use' (SANTE-2017-11668), published 22-NOV-2019. The daily SBEβCD exposure associated with administration of posaconazole IV at maintenance dose of 6 mg/kg QD is below the 200 mg/kg/day threshold in the EMA guidance. The exposure to SBEβCD for those who weigh >50 kg is less than 133 mg/kg/day as the maximum daily dose of posaconazole IV is 300 mg, QD.

In support of a regulatory authority request to contribute data on paediatric cyclodextrin use, for which paediatric clinical trial data are lacking, the PK of SBEβCD was assessed as an exploratory objective in P097. After IV administration of posaconazole 3.5, 4.5, or 6.0 mg/kg/day up to a maximum of 300 mg/day, the steady state plasma PK parameter values of SBEβCD were highly variable, but exposure increased with increasing posaconazole dose and was generally similar in both age groups within each dose cohort. No apparent pattern to suggest a dose-related difference in the safety profile was observed in P097. The incidence of drug-related AEs by posaconazole dose was 11.4%, 25.8%, and 10.2% for the 3.5, 4.5, and 6 mg/kg cohorts (equivalent to 78, 100, and 133 mg/kg SBEβCD), respectively. There were no drug-related events of renal toxicity or increased creatinine, reported in P097.

The CHMP noted that there were no drug-related events of renal toxicity or increased creatinine reported in P097.

To be noted, in procedure EMEA/H/C/000610/II/0057 for Noxafil, for the important identified risk "renal effects of cyclodextrin with IV infusion of posaconazole", there were no reports of renal failure associated with intravenous infusion of posaconazole in the clinical development of posaconazole IV formulation and there has been only one post-marketing report of renal failure requiring continuous renal replacement therapy after receiving posaconazole IV infusion in the Company's global safety database. Moreover, a routine risk minimization measure via product labelling is already mentioned in the PI. Consequently, the MAH's proposal to remove this safety concern from the RMP was accepted.

- Palatability and Acceptability of PFS Formulation in Paediatric Patients

The palatability and acceptability of the PFS formulation of posaconazole were assessed by questionnaire filled out by a nurse or primary caregiver for Age Group 1, and by the subject for Age Group 2, on Day 1 and Day 3-5 of PFS therapy and at the End of Treatment visit in P097. Taste was assessed as "average," "good," or "very good" by the majority of assessors for both age groups and for all doses at all time points. The majority of subjects in both age groups and for all doses at all time points did not report any problems taking the PFS dose. A minority of subjects experienced transient problems including refusing or spitting out the dose, vomiting or spitting up, and gagging. The proportion of subjects that experienced any of these problems in the 6 mg/kg dose cohort was 24% (6/25), 12% (2/17) and 12% (2/17) at Day 1, Day 3-5, and End of Treatment, respectively. The majority of subjects administered the posaconazole PFS formulation found the oral formulation to be palatable and acceptable.

2.6.8.6. Safety related to drug-drug interactions and other interactions

DDIs were not specifically evaluated in P097.

2.6.8.7. Discontinuation due to adverse events

The overall rate of discontinuation due to AE in the combined population was 19.9%, similar to rates reported in adult studies (18% in P05615 with posaconazole tablet and 19% in P05520 with posaconazole IV formulation).

The CHMP acknowledged that the overall rate of discontinuation due to AE in the combined population was 19.9%, indeed similar to rates reported in adult studies.

2.6.8.8. Post marketing experience

Posaconazole has been registered and approved for use in adults in more than 70 countries since its first approval on 25-OCT-2005. Currently there are 3 marketed formulations of posaconazole: oral suspension, delayed-release tablet, and concentrate for solution for IV infusion. There are no records of any registration being revoked or withdrawn for safety reasons. The benefit-risk information on posaconazole received by the MAH's AE reporting and review system has been summarized in the PSUR on an annual basis since 2006.

Cumulative post-marketing exposure for posaconazole was calculated from information provided by IMS Health, the MAH's internal distribution data from the Worldwide Financial Reporting System, and the Financial Sharing Area databases. Total cumulative patient exposure for posaconazole through 25-OCT-2019 was approximately 107,572 patient-years of treatment (46,987 for the OS, 59,590 for tablets, and 995 for the IV formulation).

As of 25-OCT-2019, there were 6240 AE reports containing 13,091 events (7725 nonserious, 5366 serious) from spontaneous and non-interventional post-marketing study reports in the Company's global safety database.

The SOCs in which AEs were most frequently reported were General disorders and administration site conditions (2630 cases); Injury, poisoning and procedural complications (2019 cases); and Infections and infestations (992 cases).

The most frequently reported PTs in the General disorders and administration site conditions SOC were adverse event (n=550 cases), death (n=497 cases), no adverse event (n=362 cases), and drug ineffective (n=348 cases). The other PTs reported in this SOC reflect the critically ill nature of patients receiving posaconazole.

The most frequently reported PTs in the Injury, poisoning and procedural complications SOC were off-label use (n=771 cases), product dose omission (n=355 cases), product use in unapproved indication (n=312 cases), and product use issue (n=143 cases).

The most frequently reported PTs in the Infections and infestations SOC were pneumonia (n=140 cases), fungal infection (n=110 cases), sepsis (n=68 cases), and septic shock (n=55 cases). These and other PTs reported in this SOC reflect the critically ill nature of patients receiving posaconazole.

A separate analysis of post-marketing reports of posaconazole use in patients under the age of 18 years within the MAH's global safety database (cumulative of 25-OCT-2019), as well as literature reports of posaconazole use in paediatric patients, revealed a similar safety profile as the general population, including the frequency of renal events.

A cumulative analysis of post-marketing AEs, as of 25-OCT-2019, did not identify new safety issues for posaconazole. The safety profile revealed by the current analysis is consistent with those presented in PSURs submitted to date and those in the product label. The overall benefit-risk balance for posaconazole

continues to be positive for use in the approved indications. The MAH will continue to monitor the safety of posaconazole through established routine pharmacovigilance processes.

- *Ovierview of AE Reports in Paediatric Patients*

There were 465 reports identified (162 non-interventional study reports and 303 spontaneous). The 465 reports contained 1152 events: 367 (32%) were considered serious and 785 (68%) were nonserious. Of the 465 reports, 180 were female patients, 259 were male patients, and 26 were of unidentified gender. With regard to age, 29 reports concerned patients <2 years old, 153 concerned patients aged 2 to <7 years old, and 283 concerned patients 7 years to 17 years old (inclusive) (mean: 8.53, median 8 [range: 0.003-17] years).

The 3 most common historical medical conditions were: hematopoietic stem cell transplantation (34 stem cell, 19 bone marrow, and 12 allogeneic cases), acute lymphocytic leukemia (15 cases), and chemotherapy (12 cases). The 3 most common current conditions were: antifungal prophylaxis (106 cases), acute lymphocytic leukemia (86 cases), and fungal infection (49 cases). The 3 most common comedications were formulations of amphotericin B (95 cases), voriconazole (40 cases), and caspofungin (29 cases). Other commonly coadministered medicines were vincristine (28 cases), the calcineurin inhibitors (cyclosporine and tacrolimus, 18 cases), and methotrexate (14 cases). Four hundred and forty-six reports involved the oral formulations and 23 reports involved the IV formulation (4 reports involved patients who received both oral and IV formulations).

By number of events, the three most commonly affected SOCs were Injury, poisoning and procedural complications; General disorders and administration site conditions; and Investigations.

The Injury, poisoning and procedural complications SOC contained 409 (36%) of all events: 9 were considered serious and 400 were considered nonserious. By number of events (n, % of all events), the three most common PT in this SOC were: off-label use (197 events, 17%), product use issue (77 events, 7%) and product administered to patient of inappropriate age (45 events, 4%). The majority of these events pertained to posaconazole being used outside of the labelled paediatric use.

The General disorders and administration site conditions SOC contained 151 events (13%): 47 were considered serious and 104 nonserious. By number of events (n, % of all events), the three most common PTs in this SOC were pyrexia (35 events, 3%), drug ineffective (21 events, 2%) and drug interaction (20 events, 2%). These AEs are not unexpected as pyrexia is inherent to the diseases being treated in this population, and the azole antifungal agents as a class are not 100% efficacious in preventing or treating IFI. The drug interaction events involved drugs known to interact with posaconazole (such as vincristine and acid reducing medications).

The Investigations SOC contained 113 (10%) of all events; 19 were considered serious and 94 nonserious. By number of events (n, % of all events), the three most common AEs in this SOC were blood potassium decreased (18 events, 2%), drug level below therapeutic (9 events, 1%), and drug level decreased and drug level increased (7 events, 1% for each).

There were 27 fatal cases (39 events due to multiple causes). Among the 27 fatal reports, 16 were spontaneous and 11 were non-interventional study cases. The most commonly reported adverse events (PTs) with fatal outcome were: sepsis (or septic shock, Klebsiella sepsis) and multiple organ dysfunction syndrome (7 cases), fungal infection (or Aspergillus infection, Candida infection, central nervous system fungal infection, mucormycosis, systemic Candida) (8 cases), drug ineffective (5 cases) and disease progression (2 cases). No cause(s) of death were listed in 8 reports; 5 of those 8 children had haematological malignancy, 2 had invasive mycosis, and 1 did not have any concomitant illness or cause of death listed.

A review of adverse events reported in the paediatric population received from post-marketing use did not identify new safety issues.

2.6.9. Discussion on clinical safety

The analysis of the combined AE data and exposure-safety relationship from studies P032 and P097 demonstrates that the posaconazole IV and PFS formulations are generally well tolerated in the paediatric population aged 2 years and above. The safety profile of posaconazole IV and PFS observed in the two studies is consistent with that described in the product label.

Previous studies with posaconazole in adults found no correlation between posaconazole exposures and safety profile across the range of posaconazole exposures observed/reported. Based on the range of the concentrations (Cavg) achieved across the dose regimens/formulations evaluated in the 2 paediatric trials, exposure-response assessments (such as a quartile analysis of drug-related AEs by steady-state Cavg concentrations for posaconazole) provide a scientifically robust method to assess the potential for exposure dependent trends. The lack of trends observed between drug-related AEs and the mean posaconazole Cavg in the pooled population of participants in P097 and P032 is consistent with that observed in adults.

The evaluation of post-marketing experience indicates that, whether used for treatment or prophylaxis, posaconazole is generally well tolerated in paediatric patients under 18 years of age.

2.6.10. Conclusions on the clinical safety

The analysis of safety data and exposure-safety relationships from prospective clinical studies (P032 and P097), literature reports of observational studies, and AE reports from post-marketing use demonstrate the overall safety profile of posaconazole in the paediatric population is similar to that established for posaconazole in adults.

2.7. Risk Management Plan

The MAH submitted an RMP version 17.2 (data lock point 25 October 2019, dated 10 May 2021) with this application to support the line extension for a new Gastro-Resistant Powder for Oral Suspension (PFS) formulation and the proposal to expand the indication for Noxafil to include paediatric patients from 2 to <18 years of age.

2.7.1. Safety concerns

The MAH proposed the following summary of safety concerns in the RMP:

Table 25: Summary of safety concerns

Summary of safety concerns	
Important identified risks	**Hepatic** – Elevated Liver Enzymes; Hepatotoxicity; Hepatic Failure; Hepatitis **Blood** – Thrombotic thrombocytopenic purpura; Haemolytic uremic syndrome **Cardiac** - Torsade de Pointes **Cardiac** – QTc prolongation **General –** Drug Interactions

Summary of safety concerns	
	Endocrine – Adrenal Insufficiency **Metabolisms** – Hypokalaemia
Important potential risks	**Cardiac –** Heart Failure; Myocardial Infarction **CNS –** Convulsion **Respiratory –**Pulmonary haemorrhage **Vascular –** Venous thrombosis; Hypertension **Visual –** Photopsia; Visual brightness; Visual disturbances
Missing information	**Experience in Children** **Use in patients with hepatic impairment**

Discussion on safety specification

Safety concerns were evaluated in the procedure EMEA/H/C/000610/II/0062. According to this procedure the MAH will modify the safety concerns accordingly.

Moreover, the following safety concerns were added:

- Medication error – related to substitution between different formulations (oral suspension and powder for oral suspension).

The missing information experience in children was replaced by safety in children below 2 years of age.

Conclusions on the safety specification

Having considered the data in the safety specification, the following issues were addressed:

- "Medication error – related to substitution between different formulations (oral suspension and powder for oral suspension)" was added as a safety concern.

The following safety concern "Experience in Children" was replaced by "Safety in children below 2 years of age".

2.7.2. Pharmacovigilance plan

Since a newly PFS formulation is introduced with non-interchangeability between the already existing Noxafil Gastro-Resistant Powder and Solvent for Oral Suspension and Noxafil Oral Suspension risk minimisation measures a one-time DHPC letter was requested to the MAH in order to inform healthcare professionals about this newly PFS formulation and the associated risk of medication error. It was asked to the MAH that the packaging should also alert HCP to avoid medication error. A DHPC communication plan was also requested to the MAH.

Subsequent to the MAH responses, providing all requested information, the PRAC considered that the MAH updated the Part VI "Summary of activities in the risk management plan by medicinal product" satisfactorily.

2.7.3. Risk minimisation measures

The PRAC considered that the following additional risk minimisation measures were necessary for the safe and effective use of the product:

A one-time DHPC addressing the potential risk of medication error related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension) as these two formulations are not interchangeable.

The MAH included the DHPC in Annex 6 of the RMP, along with list of DHPC recipients as listed in the DHPC communication plan, as requested.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 17.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Significance of paediatric studies

Study PN097, which is contained in the agreed Paediatric Investigation Plan, P/0101/2020, has been completed after 26 January 2007, is considered as significant.

2.10. Product information

CHMP has adopted an extension to the existing indications for Noxafil gastro-resistant tablets and Noxafil concentrate for solution for infusion as follows (New text as bold):

- Noxafil gastro-resistant tablets **are indicated for use in the treatment of the following fungal infections in paediatric patients from 2 years of age weighing more than 40 kg and adults (see sections 4.2 and 5.1):**
    - **Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;**
    - Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
    - Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
    - Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

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

Noxafil gastro-resistant tablets are also indicated for prophylaxis of invasive fungal infections in the following **paediatric** patients **from 2 years of age weighing more than 40 kg and adults (see sections 4.2 and 5.1):**

- Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (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.

- Noxafil concentrate for solution for infusion **is indicated for use in the treatment of the following fungal infections in adult and paediatric patients from 2 years of age (see sections 4.2 and 5.1):**

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

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

Noxafil concentrate for solution for infusion is also indicated for prophylaxis of invasive fungal infections in the following **adult and paediatric** patients **from 2 years of age (see sections 4.2 and 5.1):**

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

The CHMP also approved a new pharmaceutical form (gastro-resistant powder and solvent for oral suspension) for paediatric population with the following indications:

Noxafil gastro-resistant powder and solvent for oral suspension is indicated for use in the treatment of the following fungal infections in paediatric patients from 2 years of age (see sections 4.2 and 5.1):

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

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

Noxafil gastro-resistant powder and solvent for oral suspension is indicated for prophylaxis of invasive fungal infections in the following paediatric patients from 2 years of age:

- **Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high-risk of developing invasive fungal infections;**

- **Haematopoietic 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.**

Please refer to the Summary of Product Characteristics of Noxafil concentrate for solution for infusion and the gastro-resistant tablets for use in primary treatment of invasive aspergillosis.

Please refer to the Summary of Product Characteristics of Noxafil oral suspension for use in oropharyngeal candidiasis.

As a result of this procedure, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC, as well as the corresponding sections of the package leaflet, are updated.

Annex II was also amended to include a new batch release site (N.V. Organon, Kloosterstraat 6, 5349 AB Oss, The Netherlands), added as the manufacturing site responsible for the batch release of the new pharmaceutical form: gastro-resistant powder and solvent for oral suspension.

2.10.1. User consultation

The Package Leaflet for Noxafil 300mg gastro-resistant powder and solvent for oral suspension was adapted from that for the existing Noxafil formulations, with the addition of Instructions for Use to provide guidance on how to take the powder and solvent for oral suspension. On behalf of the MAH, a contractor conducted a User Test in line with the EU guidance. Methodology and quality aspects were in accordance with readability requirements.

The results of User Testing demonstrated that at least 90% of the participants were able to find each point of information. It also showed that at least 90% of those participants were able to understand the information. Overall, the outcome of the user testing for the patient leaflet is considered positive.

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Invasive fungal infection (IFI) is a leading cause of infectious disease morbidity and mortality in immunocompromised patients, especially in those considered at high risk for severe and prolonged neutropenia or those who have received HSCT. As in adults, the paediatric patients at risk for developing IFI, primarily due to neutropenia and T-cell dysfunction, include, but are not limited to, allogeneic stem cell transplant recipients, and patients with acute leukemias, myelodysplasia, severe aplastic anemia, and advanced-stage non-Hodgkin lymphoma. The most common IFI in these immunocompromised children are aspergillosis, candidiasis and mucormycosis.

Posaconazole 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;

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

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

- Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (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.

As a result of this paediatric extension of indication and the introduction of a new oral formulation (PFS), posaconazole (with the exception the oral suspension) will be indicated in children from 2 years of age for the prevention and treatment of fungal infections, including IFI, with an expected decrease of mortality.

3.1.2. Available therapies and unmet medical need

Several antifungal agents are approved for antifungal prophylaxis or treatment in children. These include triazoles (fluconazole, itraconazole, posaconazole and voriconazole), lipid amphotericin B, and echinocandins (caspofungin and micafungin), each with their own benefits and risks. The choice of antifungal prophylaxis or treatment for paediatric patients is limited by side effects profiles, drug-drug interactions and PK characteristics. More agents and studies on existing agents are needed.

3.1.3. Main clinical studies

This paediatric extension is based on the PK bridge study P097. This is a Phase 1b, non-randomized, multicenter, open-label, sequential dose-escalation study, with 3 doses cohorts (3.5, 4.5 and 6 mg/kg/day) of POS IV or oral (new formulation PFS). Overall, 115 immunocompromised children (2 to <18 years old) were treated with POS for prophylaxis of IFI.

3.2. Favourable effects

The use of a 6 mg/kg dose of POS (IV or PFS) in paediatric subjects from 2 years of age is associated to an adequate POS exposure, within the endorsed Cavg target between 500 and 2500 ng/mL. The use of a 300 mg dose with the POS tablet formulation for paediatric patients over a weight of 40 kg is also endorsed as regards this PK target attainment.

3.3. Uncertainties and limitations about favourable effects

Study P097 was not designed to assess clinical efficacy of POS for the prophylaxis of IFI in paediatric immunocompromised patients. This is not an efficacy study, there is no comparison of POS vs an active comparator (such as voriconazole).

With the initially proposed dose of 6mg/kg, a non-negligible percentage of paediatric subjects from 2 to <7 years old (6.8%) is predicted to have a Cavg below the target of 500 ng/mL, and therefore be potentially treated with a suboptimal POS dose.

However, with the increased dose for the age group with body weight of 10-30kg of 8mg/kg, a Cavg above 500ng/ml, only a predicted 1.4% of patients 10 to 30kg will reach a Cavg below the 500ng/ml target.

3.4. Unfavourable effects

The analysis of the combined AE data and exposure-safety relationship from studies P032 and P097 demonstrates that the posaconazole IV and PFS formulations are generally well tolerated in the paediatric population aged 2 years and above. The safety profile of posaconazole IV and PFS observed in the two studies is consistent with that described in the product label.

The overall rate of drug-related SAEs (1.6%) was low in the combined pool and in the individual studies. This low rate is similar to overall rates of drug-related SAEs reported in adult studies (3% in P05615 with posaconazole tablet and 1% in P05520 with posaconazole IV formulation. No individual drug-related SAE was reported in >1 subject in either treatment group.

3.5. Uncertainties and limitations about unfavourable effects

To ensure proper use of the newly introduced PFS formulation, the product labelling and package carton will clearly state that Noxafil OS and Noxafil PFS are not to be used interchangeably. However, an oral suspension already exists and is not interchangeable, especially there is a risk of confusion between these formulations leading to potential dosing error. Such switch may therefore lead to possible risks associated with patients receiving incorrect formulation and/or dose of posaconazole include either lack of efficacy due to subtherapeutic drug levels, or drug toxicity due to supratherapeutic drug levels". The current SmPCs, packagings, and leaflets already contain warnings on Non-Interchangeability between Noxafil Tablets and Noxafil Oral Suspension, and a DHPC had been sent at the time when this issue arose. In line with these previous measures, a one-time DHPC letter and warnings in the product information (including the packaging) will be disseminated prior to launching the PFS formulation in order to prevent potential medication errors.

3.6. Effects Table

Not relevant for this PK bridging application.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

With the new paediatric PFS formulation, an oral POS regimen is available to ensure an adequate POS exposure within the therapeutic range, and therefore an effective antifungal activity for a prophylactic

or curative treatment of IFI in immunocompromised children from 2 years of age. The IV formulation is also concerned by this paediatric extension.

A new PFS formulation is introduced. To ensure proper use of the newly introduced PFS formulation, the product labelling and package carton will clearly state that Noxafil OS and Noxafil PFS are not to be used interchangeably. However, in order to prevent medication errors, a one-time DHPC letter will be disseminated and warnings introduced in the product information (including the packaging).

3.7.2. Balance of benefits and risks

With the new PFS paediatric formulation and the proposed dosing regimen, children from 2 years of age will benefit of a treatment for the prophylaxis and treatment of IFI, similarly to the adult population. Although no efficacy data were available in this paediatric population, it has been demonstrated through a PK bridge study than POS exposure with this new oral formulation is similar to that observed in adults and within the therapeutic range. In order to attain a target Cavg of more than 500 ng/ml, a different dosing regimen is proposed based on body weight: 8mg/kg for paediatric patients of 10-30kg bw and respectively 6mg/kg for patients 31-40 kg bw.

The safety profile of POS observed in this paediatric population is consistent with that described in the product information. As another POS oral formulation is available on the market, the potential risk of confusion and dosing error between these formulations is mitigated by clear information in the product literature and dissemination of a one-time DHPC.

In conclusion, considering the limited available therapeutic options for the prevention and treatment of IFI in paediatric subjects, and the high mortality rate of such infections, the benefit-risk balance for this paediatric extension is considered positive.

3.8. Conclusions

The overall benefit/risk balance of Noxafil is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP, by consensus, is of the opinion that Noxafil is not similar to isavuconazonium sulfate within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Noxafil 300 mg gastro-resistant powder and solvent for oral suspension (PFS) is favourable in the following indications:

Noxafil gastro-resistant powder and solvent for oral suspension is indicated for use in the treatment of the following fungal infections in paediatric patients from 2 years of age (see sections 4.2 and 5.1):

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

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

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

Noxafil gastro-resistant powder and solvent for oral suspension is indicated for prophylaxis of invasive fungal infections in the following paediatric patients from 2 years of age:
- **Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high-risk of developing invasive fungal infections;**
- **Haematopoietic 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.**

CHMP also adopted an extension to the existing indications for Noxafil gastro-resistant tablets and Noxafil concentrate for solution for infusion as follows (New text as bold):

- Noxafil gastro-resistant tablets **are indicated for use in the treatment of the following fungal infections in paediatric patients from 2 years of age weighing more than 40 kg and adults (see sections 4.2 and 5.1):**
  - **Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;**
  - Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
  - Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
  - Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

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

Noxafil gastro-resistant tablets are also indicated for prophylaxis of invasive fungal infections in the following **paediatric** patients **from 2 years of age weighing more than 40 kg and adults (see sections 4.2 and 5.1):**
- Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (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.

- Noxafil concentrate for solution for infusion **is indicated for use in the treatment of the following fungal infections in adult and paediatric patients from 2 years of age (see sections 4.2 and 5.1):**
  - **Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;**
  - Fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B;
  - Chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole;
  - Coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products.

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

Noxafil concentrate for solution for infusion is also indicated for prophylaxis of invasive fungal infections in the following **adult and paediatric** patients **from 2 years of age (see sections 4.2 and 5.1):**

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

The CHMP therefore recommends the extensions of the marketing authorisation for Noxafil 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 requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 Marketing authorisation holder (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.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMEA-000468-PIP02-12-M06 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Variations		**Type**	**Annexes affected**
X.02.IV	Annex I_2.(d) Change or addition of a new pharmaceutical form	Line Extension	I, II, IIIA, IIIB and A
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I, IIIA and

	of a new therapeutic indication or modification of an approved one		IIIB

Extension application to introduce a new pharmaceutical form (gastro-resistant powder and solvent for oral suspension), grouped with a type II variation (C.I.6.a) to extend the approved indications to the paediatric population for Noxafil gastro-resistant tablets and Noxafil concentrate for solution for infusion.

As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC, as well as Annex II and the package leaflet, are updated.

The RMP (version 18.0) is approved with this procedure.