29 January 2026
EMADOC-1700519818-2632882
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Noxafil

International non-proprietary name: Posaconazole

Procedure No. EMA/VR/0000263360

Note

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

Table of contents

List of abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AMB	amphotericin B
APaT	all participants as treated
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BW	body weight
Cavg	average plasma concentration
CI	confidence interval
CL	clearance
Cmax	observed maximal concentration
Cmin	observed minimal concentration
CSR	clinical study report
DDI	drug-drug interaction
DILI	drug-induced liver injury
EBE	empirical Bayes estimate
ECG	electrocardiogram
ECI	events of clinical interest
EMA	European Medicines Agency;
EORTC/MSG	European Organisation for Research and Treatment of Cancer/Mycoses Study Group
E-R	exposure response
EU	European Union
FAS	full analysis set
FDA	Federal Drug Administration
IA	invasive aspergillosis
IFI	invasive fungal infection
IV	Intravenous

PFS	powder for suspension (gastro-resistant powder and solvent for oral suspension)
PIP	paediatric investigation plan
PK	pharmacokinetic(s)
popPK	population PK
POS	posaconazole, MK-5592, NOXAFIL®
QTc	corrected QT interval
SAE	serious adverse event
US	United States
Vc	volume of the central compartment
VOR	Voriconazole

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, on 27 March 2025, Merck Sharp & Dohme B.V. submitted to the European Medicines Agency an application for a variation.

The following changes were proposed:

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

Extension of indication for NOXAFIL to include treatment of patients two years of age and older for invasive aspergillosis (IA) based on final results from study MK-5592-104 (P104); this is a Phase 2, open-label, noncomparative clinical study that evaluated the safety, efficacy, and PK of POS in paediatric participants aged 2 to <18 years with IA. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 18.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the PI.

The variation requested amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0376/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0376/2024 was not yet completed.

GLP/GCP inspections

Not applicable.

Information relating to orphan market exclusivity

Not applicable.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

It is considered that Noxafil is not similar to Cresemba (isavuconazole), taking into account Article 3 of Commission Regulation (EC) No. 847/2000.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Nicolas Beix

Timetable	Actual dates
Submission date	27 March 2025
Start of procedure:	26 April 2025
CHMP Rapporteur's preliminary assessment report circulated on:	20 June 2025
Joint Rapporteur's updated assessment report circulated on:	17 July 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2025
MAH's responses submitted to the CHMP on:	04 September 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	14 October 2025
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	07 November 2025
Request for 2nd supplementary information and extension of timetable adopted by the CHMP on:	13 November 2025
MAH's responses submitted to the CHMP on:	17 December 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	14 January 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	22 January 2026
CHMP opinion:	29 January 2026
The CHMP adopted a report on similarity of Noxafil with Cresemba on (Appendix 1):	29 January 2026

2. Scientific discussion

2.1. Introduction

At the time of submission of this application, NOXAFIL (posaconazole, or POS) was authorised in the EU for the prophylaxis of Invasive Fungal Infections (IFI) and treatment of refractory IFIs in patients 2 years of age and older, and for the primary treatment of Invasive Aspergillosis (IA) in adult patients. Approved POS formulations include an IV solution and 3 oral formulations: oral suspension, powder for suspension (PFS) and tablets.

2.1.1. Problem statement

Disease or condition

Aspergillus species are filamentous fungi, commonly found in the environment, that can cause a wide spectrum of infections in humans; these infections, such as Invasive Aspergillosis, can be acute and life-threatening, primarily in immunocompromised individuals.

State the claimed the therapeutic indication

The purpose of this variation is to extend the indication for the primary treatment of Invasive Aspergillosis to paediatric patients 2 years of age and older.

Epidemiology and risk factors, screening tools/prevention

Invasive Aspergillosis infections occur in paediatric (and adult) populations that are immunocompromised due to various factors (e.g., malignancy, solid organ transplant or hematopoietic stem cell transplant, and primary immunodeficiency) and play a significant role in the morbidity and mortality observed in these populations; A retrospective cohort study reported that the incidence of IA among hospitalized immunocompromised children <18 years of age in the US was between 0.1% and 30%. A 2021 study in the EU estimated the prevalence of IA among immunocompromised children to be 2.2%. Following an initial diagnosis of IA, immunocompromised children in the US had a 12-week and 1-year all-cause mortality rate of 25.4% and 40.7%, respectively, in 2019.

Clinical presentation, diagnosis and stage/prognosis

Invasive aspergillosis is the third clinical presentation of Aspergillus infection in the lung. This is the most life-threatening manifestation of Aspergillus infection, occurring almost exclusively in patients with marked impairment of host immune defence mechanisms. The most important risk factor is neutropenia (insufficient numbers of polymorphonuclear leukocytes), but patients often also have impairment of cellular immunity as a consequence of treatment with chemotherapeutic agents.

Pathologically, the organism invades and spreads through lung tissue. However, it also tends to invade blood vessels within the lung. As a result of vascular involvement by the fungus, haemoptysis can occur, vessels can become occluded, and areas of pulmonary infarction can develop.

Clinically, patients are extremely ill, with fever, cough, dyspnoea, and often pleuritic chest pain. The chest radiograph may show localized or diffuse pulmonary infiltrates, reflecting either tissue invasion and a fungal pneumonia or pulmonary infarction secondary to vascular occlusion.

According to EORTC definition, IA could be classified in three categories as possible, probable or proven IA. Proven invasive fungal infection requires only that a fungus be detected by histological analysis or culture of a specimen of tissue taken from a site of disease. By contrast, probable and possible invasive fungal infections hinge on 3 elements: namely, a host factor that identified the patients at risk, clinical signs and symptoms consistent with the disease entity, and mycological evidence that encompassed culture and microscopic analysis but also indirect tests, such as antigen detection. These EORTC/MSG Consensus Group definitions have been used in major trials of antifungal drug efficacy, in strategy trials, for the formulation of clinical practice guidelines, for validation of diagnostic tests, and for performance of epidemiologic studies.

Management

Current guidelines for the management of IA in adult patients recommend voriconazole (VOR) for the primary treatment of invasive pulmonary aspergillosis, with POS, isavuconazole, or lipid formulations of amphotericin B as second line or alternative therapies. However, there is a paucity of prospective study data in the paediatric population. Therefore, the evaluation of treatment options for IA in the paediatric population is warranted.

2.1.2. About the product

Posaconazole (POS, also known as MK-5592, NOXAFIL®) is a highly active triazole. POS (IV, PFS, and tablet formulations) has been approved for use in children 2 to <18 years of age for the prophylaxis and salvage treatment of IFIs based on data from a prospective PK and safety study that evaluated POS IV and PFS in children 2 to 17 years of age who were at high risk of an IFI. The approved indications and patient populations vary by country.

2.1.3. The development programme/compliance with CHMP guidance

Prior to this extension of indications application for the treatment of IA in paediatric patients, POS IV and tablets were studied for the treatment of IA in adults and adolescents in a pivotal Phase 3, multicentre, randomized, double-blind, active-comparator study: MK-5592-069 (hereafter referred to as P069). The efficacy and safety of POS in P069 demonstrated the non-inferiority of POS to VOR in participants with IA, supporting the indication for the primary treatment of IA.

Additionally, another previous application to support the approval of indications in children and adolescents (aged 2 to <18 years) for prophylaxis of IFIs and treatment of refractory IFIs, provided the PK and safety results of two Phase 1b paediatric studies of POS (MK-5592-097 [hereafter referred to as P097] and MK-5592-032 [hereafter referred to as P032]).

Another Phase 2 paediatric study (MK-5592-127 [hereafter referred to as P127]), being conducted in paediatric participants from birth to <2 years of age with IFI was ongoing at the time of this report.

This extension of indications application for the treatment of IA to paediatric patients 2 years of age and older includes results from a Phase 2 study: MK-5592-104 [hereafter referred to as P104].

2.1.4. General comments on compliance with GCP

The clinical studies were conducted in accordance with current standard research approaches with regard to the design, conduct, and analysis of such studies including the archiving of essential documents. All studies were conducted following appropriate Good Clinical Practice standards and considerations for the ethical treatment of human participants that were in place at the time the studies were performed.

2.2. Non-clinical aspects

With this application, the MAH proposed to extend the indications to paediatric patients 2 years and older for the treatment of invasive aspergillosis, for the gastro-resistant tablets, concentrate for solution for infusion, and gastro-resistant powder and solvent for oral suspension.

POS is approved for prophylaxis of IFIs and treatment of refractory IFIs in patients 2 years of age and older. At the time of this application, POS was also approved in the EU for the primary treatment of IA in adults. Approved POS formulations include an IV solution and 3 oral formulations (oral suspension, PFS, and tablet).

The CHMP noted that the approval of POS for the treatment of IA in paediatric patients was supported by the comprehensive non-clinical programmes (including juvenile toxicological studies) previously conducted for the existing POS oral and IV formulations, as was agreed in the context of the Noxafil PIP. Therefore, it was acceptable that no additional non-clinical studies were conducted to support the extension of indication applied for.

2.2.1. Ecotoxicity/environmental risk assessment

The purpose of this application is to extend the approved indication for POS (as IV, PFS, and tablet) for the primary treatment of IA in paediatric patients 2 years of age and older.

A refined percentage of market penetration (FPEN-REFINED) is derived based on prevalence data.

The estimated disease burden in Europe, in accordance with the different therapeutic indications (see Table 1), is 397,200 subjects for a one-year period. This includes both adult and paediatric patients and results in a refined market penetration (FPEN-REFINED) of 0.0764% (397,200 patients out of the population of 520,000,000 for the European Union (EU281 2024), including Norway, Iceland, and Liechtenstein (Eurostat 2024)).

The estimated disease burden was not adjusted for alternative treatment options, nor for severity of disease, nor adjusted for market uptake. In addition, adjustments were not made to the estimated disease burden for the possibility of double counting and individuals with invasive aspergillosis refractory to amphotericin B or itraconazole.

Individuals may be counted in more than one treatment or risk groups. For example, individuals could have acute myeloid leukemia, and either be an allogenic hematopoietic stem cell transplant recipient or have invasive aspergillosis.

Table 1 Estimated European Population with Potential Exposure to Posaconazole

Indication		Estimated Size of Population (N) in 2024	Reference
Treatment	Invasive Aspergillosis	64,000[a]	[3]
	Fusariosis	264[b] [Incidence: 6/1000 for HSCT (44,000 allogenic and autologous)]	[4] [5]
	Chromoblastomycosis and mycetoma[c]	Rare[d]	[6] [7] [8]
	Coccidioidomycosis[c]	Rare[d]	[8] [9]
	Oropharyngeal candidiasis[e]	Estimated 127,000 oral candidiasis and 82,200 oesophageal candidiasis[f]	[8]
Prophylaxis	Acute Myeloid Leukemia	55,000[a] (prevalence; 19,000 incidence)	[10]
	Hematopoietic Stem Cell Transplant	44,000 allogenic and autologous HSCTs per year (approximately 42% allogeneic)	[5]
	Myelodyspastic Syndrome [23]	25,000[a] (prevalence; 8,000 incidence)	[10]
Total Population		397,200	

[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) [11] [12].

[f] This is based on estimated 2 million and 1.3 million global incidence of oral candidiasis and oesophageal candidiasis and prorated to EU28 2024 (including the UK), Norway, Iceland and Liechtenstein.

Taking into account these new prevalence data, a PECsw was calculated. Results from phase I and phase II studies are reported in the following tables.

Table 2 Summary of main study results: Phase I

Substance (INN/Invented Name):	*Noxafil (Posaconazole)*		
CAS-number (if available):	*171228-49-2*		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion

Bioaccumulation potential-log Kow	OPPTS 830.7560	*4.06 at pH 5* *4.15 at pH 7* *4.10* at pH *9*	Potential PBT: *N*
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	*log* k_{ow}	*4.06 at pH 5* *4.15 at pH 7* *4.10* at pH *9*	not B
	BCF_{kgl}	*29-36* L/kgww	Not B
Persistence	Ready biodegradability	N	potentially P
Toxicity	$NOEC_{aquatic}$	*0.041* mg/L *(green algae, Pseudokirchneriella subcapitata)*	not T
PBT/vPvB statement:	*Noxafil (Posaconazole)* is considered to be not PBT, nor vPvB		

Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
PEC_{sw}, *refined Prevalence*	*0.3*	µg/L	≥ 0.01 threshold: *Y*
Other concerns (e.g. chemical class)			N

Table 3 Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	*2.54* mg/L at *20 °C*	Column elution method
Adsorption-Desorption Soil 1 = *clay loam*	OECD 106	$K_{FOC, soil\ 1}$ = *149,537* L/kg_{oc}	
Soil 2 = *sandy clay loam*		$K_{FOC, soil\ 2}$ = *63,143* L/kg_{oc}	
Soil 3 = *sandy loam*		$K_{FOC, soil\ 3}$ = *97,605* L/kg_{oc}	
Soil 4 = *Montana clay loam*		$K_{FOC, soil\ 4}$ = *125,751* L/kg_{oc}	
Sludge 1 = *from Cambridge Wastewater Treatment Facility (USA)*		$K_{FOC, sludge\ 1}$ = *2,790* L/kg_{oc}	
Ready Biodegradability Test	OECD 301*B*	*-1.6* % *not readily biodegradable*	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = *from Choptank River (USA)*	OECD 308	$DT_{50, water\ 1}$ = *0.5* d $DT_{50, sediment\ 1}$ = *20.45* d $DT_{50, whole\ system\ 1}$ = *0.7* d	*20* °C
Sediment 2 = *from Brandywine Creek (USA)*		$DT_{50, water\ 2}$ = *4.5* d $DT_{50, sediment\ 2}$ = *21.09* d $DT_{50, whole\ system\ 2}$ = *13.3*d	*20* °C
Transformation products		>10% = *Y*	*7 degradants present in quantities >10%* *M2 et M3 are potentially persistent in sediment*
Phase II Aquatic effect studies			
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	NOEC	41	*µg*/L	*growth rate*

Daphnia sp. Reproduction Test/ *Daphnia magna*	OECD 211	NOEC	244	*µg*/L	*Immobility reproduction*
Fish, *Pimephales promelas*	OECD *210*	NOEC	206	*µg*/L	*Hatching, survival, growth*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1,000	*µg*/L	*Total respiration*
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD *218*	NOEC	76	*mg*/kg_{dw}	*applicable endpoint(s), normalised to 10% o.c.*
Phase II Secondary poisoning					
Bioaccumulation Test/*Lepomis macrochirus* Test 1 = *8.2* µg/L Test 2 = *82* µg/L	OECD 305	$BCF_{KgL,\ 1}$ $BCF_{KgL,\ 2}$	29 36	L/kg L/kg	*Since the BCF is <100 L/kg, secondary poisoning assessment is not required.*
Risk characterisation					
Compartment	**PEC**	**PNEC**	**RQ**		**Conclusion**
STP	*3.0 µg/L*	*100,000 µg/L*	*0.00003*		No risk
Surface water	*0.30 µg/L*	*4.10 µg/L*	*0.074*		No risk
Groundwater	*0.075 µg/L*	*0.41 µg/L*	*0.18*		No risk
Sediment	*0.29 mg/kgdw*	*3.8 mg/kgdw*	*0.077*		No risk
Soil					Not required
Secondary Poisoning					Not required

2.2.2. Discussion on non-clinical aspects

The MAH did not perform any new experimental environmental studies for this extension of indications application. However, a new ERA with updated prevalence data was provided.

The data summary provided by the MAH adequately reflects the data in the actual reports.

Tables have been updated to adapt to the new template and to include the new PECsw. As it was higher than the action limit, phase II results were presented as well.

In conclusion, the risk characterisation showed no specific risk for assessed compartments.

Consequently, based on the currently available information, no further actions are necessary and no special precautionary and safety measures need to be taken for the storage, labelling, administration and disposal of posaconazole.

2.2.3. Conclusion on the non-clinical aspects

No additional non-clinical studies were conducted to support this indication, which was acceptable to the CHMP.

Considering the above data from Phase I and Phase II, posaconazole is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

This application is an extension of indication for NOXAFIL to include treatment of patients two years of age and older for invasive aspergillosis (IA), based on final results from study MK-5592-104 (P104); this was a Phase 2, open-label, non-comparative clinical study that evaluated the safety, efficacy, and PK of POS in paediatric participants aged 2 to <18 years with IA. This application does not cover the Noxafil Oral Suspension formulation.

GCP

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

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

- Tabular overview of clinical studies

Study Number (Status) [CTD Location] Number of Study Sites (Regions)	Design (Indication)	Number of Participants by Intervention Group and Age Cohort	Study Population	Endpoint
MK-5592-104 (completed) [Ref. 5.3.5.2: P104MK5592] 16 sites (9 countries) enrolled participants	Phase 2, open-label, noncomparative study of POS IV, PFS, and tablet formulations in pediatric participants aged 2 to <18 years with IA. Duration: Up to 12 weeks (84 days) Indication: Treatment of IA	All enrolled participants: **Overall**: 31 enrolled, 31 treated, 10 completed study intervention, 21 discontinued study intervention, 27 completed study, 4 discontinued study. **Age Cohort** 1 (2 to <12 years of age): 14 enrolled, 14 treated, 1 completed study intervention, 13 discontinued study intervention, 13 completed study, 1 discontinued study. **Age Cohort 2** (12 to <18 years of age): 17 enrolled, 17 treated, 9 completed study intervention, 8 discontinued study intervention, 14 completed study, 3 discontinued study	All enrolled participants: *Median Age (Range):* **Overall**: 12.0 years (2 to 17 years) **Age Cohort 1**: 8.0 years (2 to 11 years) **Age Cohort 2**: 14.0 years (12 to 17 years) *Sex:* **Overall**: 23 (74.2%) male, 8 (25.8%) female **Age Cohort 1**: 7 (50%) male, 7 (50%) female **Age Cohort 2**: 16 (94.1%) male, 1 (5.9%) female	**Primary:** • Drug-related AEs **Secondary:** • Global clinical response (partial or complete response) as per EORTC/MSG definitions • Relapse of IA, defined as the re-emergence of clinical, radiographic, or other relevant abnormalities indicating IA • Key PK parameters, consisting of C_{avg}, C_{min}, C_{max}, AUC, and T_{max}, using sparse plasma concentration sampling (steady-state trough and peak) • Analysis of exposure-response (efficacy and safety) relationships • Participants' categorical perception of the taste of the PFS formulation
AE=adverse event; AUC=area under the concentration-time curve; C_{avg}=average plasma concentration; C_{max}=observed maximal concentration; C_{min}=observed minimal concentration; CTD=Common Technical Document; EORTC/MSG=European Organisation for Research and Treatment of Cancer/Mycoses Study Group; IA=invasive aspergillosis; IV=intravenous; PFS=powder for suspension (gastro-resistant powder and solvent for oral suspension); PK=pharmacokinetic(s); POS=posaconazole; T_{max}=time to maximum concentration				

2.3.2. Pharmacokinetics

Posaconazole (POS, also known as MK-5592) is a systemic triazole antifungal agent that inhibits ergosterol production, an enzyme essential for the biosynthesis of ergosterol, a key component of the fungal cell membrane. POS exhibits antifungal activity against strains that are resistant to AMB, FLZ, VOR, or ITZ.

POS is available in 4 formulations named POS OS, POS solution for injection (POS IV), POS delayed release tablet (gastro-resistant, referred as POS tablet), and POS powder for delayed-release oral suspension (gastro-resistant powder, referred as POS PFS).

The POS tablet is supplied at one strength 100 mg, and the POS IV as a solution containing 300 mg POS per 16.7 mL solution (18 mg/mL). The POS PFS is a sachet containing 300 mg of POS, however only a maximum 240 mg (8 mL) can be delivered (Table 4).

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

- POS tablet is 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 PFS tablet is absorbed with a median Tmax of 4h. Compared to POS tablet, POS PFS has a 19% increased exposure and 17% increased Cmax.
- 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.

Considering past approvals, a wealth of PK information of POS in adults is available. Hence, PK properties are considered to be well-known in adults. Consequently, this assessment report will focus on specific PK (and PD aspects) relevant for this submission.

According to the paediatric clinical development programme (EMEA-000468-PIP02-12-M09), four paediatric studies were planned (P032, P097, P104 and P127). Two paediatric clinical studies (P032 and P097) were completed in support of the application previously approved for IFI prophylaxis in paediatric patients 2 to <18 years of age.

With this application, the MAH wishes to extend the use of POS IV, POS tablet and POS PFS for the treatment of invasive aspergillosis (IA) in children aged ≥2 years, using a PK extrapolation approach. Therefore, in support of the extension, results from the clinical Phase 2 study P104 were provided, in addition to a developed Population PK analysis (PPK) and exposure-response analysis (ER).

An additional paediatric PK and safety study (P127) of POS IV and PFS for treatment of IFIs in paediatric participants aged < 2 years is ongoing. Preliminary PK data from P127 following a single POS IV dose have been included in the paediatric PPK model to provide an opportunity to comprehensively assess POS PK across a broader range of participant weight and age.

For the IA indication in children aged ≥2 years, the recommended dose for

- POS Tablet is 300 mg BID first day and 300 mg QD thereafter
- POS IV is 6m/kg BID first day then 6 mg/kg QD thereafter
- POS PFS is based on Table 1 with the weight-based dose BID the first day and the weight-based dose QD thereafter.

Table 4: Dosing recommendation (POS PFS)

Weight (kg)	Dose (volume)
10-< 12 kg	90 mg (3 mL)
12-< 17 kg	120 mg (4 mL)
17-< 21 kg	150 mg (5 mL)
21-< 26 kg	180 mg (6 mL)
26-< 36 kg	210 mg (7 mL)
36-40 kg	240 mg (8 mL)

Sections 4.1, 4.2 and 5.2 of the SmPC have been updated to reflect the above.

2.3.3. Methods

A HPLC/MS/MS assay procedure was used to quantify POS plasma concentration, using K2EDTA as anticoagulant, and was validated at Syneos Health Clinique (Quebec, QC, Canada).

POS and its stable deuterated isotope (D5-POS) as internal standard were extracted following an automated liquid-liquid extraction followed by LC-MS/MS separation and detection. The method has a calibration curve ranging from 5 to 5000 ng/mL and consisted of 8 concentration levels. Four QC were considered at 5 (LLOQ), 15 (3xLLOQ), 2500 (50% ULOQ) and 3750 (75% ULOQ) ng/mL. Inter-run and intra-run precision was below 11% and 8%, respectively. Inter and intra-run accuracy ranged from -4.8 to 10.1% and -6.4 to 24.2%, respectively. No matrix effect nor hemolyzed and lipemic matrix effects were identified. Long-term stability was demonstrated at 1226 days stored at -20°C and 918 days stored at -80°C. The validation summary is presented in Table 5.

In study validation

For study P104, a total of 238 samples were received and analysed. The maximum sample storage duration from collection to analysis was 1133 days when stored at -20°C. Samples were received from 1st Sept 2020 and 11th Jan 2024, and analysis starts from 24th May 2021 to 15th Jan 2024. Seven out of 7 runs were acceptable. Cumulative bias and precision were below 5%. Fourteen samples were re-analysed, all were near or exceeded the ULOQ and were therefore diluted. ISR were performed and showed satisfactory results (94.12%).

Table 5: Validation summary

Validation Parameters	Results
Summary of Validation Runs:	N/AP
Linearity:	$r^2 \geq 0.9954$
Calibration Curve Range:	5.00 to 5000.00 ng/mL
Calibration Curve Goodness of Fit:	Biases: -3.78 to 5.07%
Accuracy and Precision (Between):	Biases: -4.85 to 10.10% CV: 3.47 to 10.82%
Accuracy and Precision (Within):	Biases: -6.41 to 24.17%* CV: 1.50 to 7.13% *Refer to Section 4.3 for details.
Sensitivity:	Between-Run LLQC Bias: 10.10% Between-Run LLQC CV: 10.82%
Run Size Evaluation (288 samples):	Biases: -0.67 to 2.92% CV: 2.44 to 3.62%
Recovery of Analyte:	Recovery: 109.50, 95.23 and 99.35% CV: 1.46 to 8.98%
Recovery of Internal Standard:	Recovery: 91.69% CV: 0.79 and 8.16%
Dilution Integrity (Frozen Sample):	At 10000.00 ng/mL diluted 1/20: Bias: 0.05% CV: 2.48% At 24285.71 ng/mL diluted 1/20: Bias: -5.75% CV: 3.97%
Matrix Selectivity (Including Hyperlipemic Matrix and Hemolyzed Matrix at 5%):	No significant interference observed in 8 out of 8 tested matrices for MK-5592 and its IS
Potentially Interfering and Commonly Used Drugs:	No effect on the quantitation of the analyte
Matrix Effect (Including Hyperlipemic Matrix and Hemolyzed Matrix at 5%):	Mean IS-Normalized matrix factor: 0.983262 and 0.993491 CV: 2.75% and 1.26%
Matrix Effect (Spiked QCs) (Including Hyperlipemic Matrix and Hemolyzed Matrix at 5%):	No effect on the quantitation of analyte
Autosampler Carryover of Analyte and IS:	No significant carryover observed
Reinjection Reproducibility:	72h00min at room temperature
Freeze and Thaw Stability in Matrix:	4 cycles at -20°C and -80°C
Short-Term Stability of Analyte in Matrix:	23h45min at room temperature and 20h52min at 4°C
Long-Term Stability of Analyte in Matrix:	7, 918 and 1226 days at -20°C 7 and 918 days at -80°C
Stability of Analyte in Whole Blood:	240 minutes in an ice/water bath (centrifugation at 4°C) 240 minutes in an ice/water bath (centrifugation at room temperature)
Pre-Automated Extraction Stability:	22h25min at 4°C
Post-Preparative Stability:	72h00min at room temperature
Short-Term Stability of Analyte and IS in Solution (High Concentration):	25h26min at room temperature
Short-Term Stability of Analyte in Solution (Low Concentration):	24h20min at room temperature
Short-Term Stability of IS in Solution (Low Concentration):	25h26min at room temperature
Long-Term Stability of Analyte in Solution (High and Low Concentrations):	925 days at -20°C

The CHMP considered that the method developed for POS quantification was adequate and complied with ICH-M10. Description and validation reports were provided with satisfactory results regarding specificity, sensitivity, precision, dilution factor linearity and matrix effect. Short- and long-term stability were tested and showed to be satisfactory.

For accuracy, during the method development, the within-run accuracy failed to meet the acceptance criteria in one run because the mean %bias was not within ± 20% at the LLOQ level, the

MAH suspected an error in the LLOQ level preparation, this is plausible. The run was repeated but the data were not presented.

The results from the study P104 bioanalytical report are satisfactory.

2.3.4. Study P104

Study P104 was a Phase 2, open-label, non-comparative, multisite study of POS IV and oral formulations (PFS or tablet) in paediatric participants aged 2 to <18 years with IA.

The primary objective of the study was to evaluate the safety of POS administered as IV or oral formulations. The secondary objectives were to evaluate the efficacy of POS, relapse in the target population and to characterize the PK of POS overall and by formulation. A tertiary objective was to evaluate all-cause mortality in participants treated with POS.

Design

Following a screening period up to 14 days, participants who met the criteria for possible, probable or proven IA, were enrolled to receive open-label POS for a duration up to 12 weeks. All the participants received (Table 3):

- First, the IV formulation at 6 mg/kg BID first Day, and 6 mg/kg QD thereafter
- Then, after 7 days of continuous QD treatment subjects can transition to the oral formulation (PFS or tablet) for a treatment duration up to Week 12
- Further transition from POS oral to IV was allowed if needed

Table 6: Formulation and dosing schedule

Arm Name	Arm Type	Interven-tion Name	Interven-tion Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period
Posaconazole	Experi-mental	IV	Drug	Vial	18 mg/mL	6 mg/kg Doses are not to exceed 300 mg per administration	IV Infusion	Day 1: BID Day 2 through end of IV dosing: QD
Posaconazole	Experi-mental	PFS	Drug	PFS	30 mg/mL	Dosing based on weight band. To be administered to participants ≤40 kg	Oral	Days 8 – 84: QD
Posaconazole	Experi-mental	Tablet	Drug	Tablet	100 mg	300 mg To be administered to participants >40 kg	Oral	Days 8 – 84: QD

For the PFS formulation, the weight-band dosing used is the one presented in Table 4.

To achieve at least 15 participants who transitioned to oral POS, approximately 30 participants were planned to be enrolled in 2 age cohorts, simultaneously:

- Cohort 1: 2-< 12 years with approximately 20 participants
- Cohort 2: 12-<18 years with approximately 10 participants

Sparse PK sampling was performed at Day 1 and Weeks 1, 2, 4, 6, 9, 12 and consisted of steady-state peak and trough concentrations. Key PK parameters (Cavg, Cmin, Cmax, AUC and Tmax) will be determined by using a previous developed PPK model.

Results

A total of 28 subjects were enrolled in study P104, 13 in Cohort 1 and 15 in Cohort 2. Table 7 presents the summary of POS pre-dose plasma concentration by age cohort and Figure 1 the associated plot on a log scale. Table 8 presents the summary of POS at "peak" concentrations.

Mean POS Ctrough were generally similar across the 3 formulations and between the two age cohorts with Ctrough ranging from 1000 to 2000 ng/mL. Mean POS "peak" (3 to 6 h post dose) are generally similar between formulations and age cohorts and lower than those observed with the IV formulation, as expected.

Table 7: Summary of POS pre-dose by Age cohort and formulation

		Visit					
		Week 1	Week 2	Week 4	Week 6	Week 9	Week 12
		POS Predose (Trough) Plasma Concentration (ng/mL)					
Age Cohort	Formulation	GM (GCV%) [n][a]					
1 (2 to < 12 years old)	POS IV	1267 (150.1) [11]	1410 (115.7) [5]	852.9, 1704	NC	NC	NC
	POS PFS	NC	1479 (44.2) [4]	1603 (31.4) [5]	1734 (51.0) [4]	1433, 1691	1074
	POS Tablet	NC	2974	3899	3706	NC	NC
2 (12 to <18 years old)	POS IV	1475 (55.3) [13]	1778 (81.6) [6]	956.8 (28.3) [3]	799.0	830.8	NC
	POS PFS	NC	2547	1742, 2823	1391, 3918	1505, 4556	2624
	POS Tablet	NC	1586 (74.5) [7]	1620 (60.8) [7]	1831 (45.2) [8]	2014 (36.5) [7]	1452 (113.5) [8]

BLQ = below limit of quantification; GCV = geometric coefficient of variation; GM = geometric mean; IV = intravenous; n = number of observation; NC = not calculated; PFS = powder for suspension; POS = posaconazole.
Note: On Day 1, all participants were given POS IV (n=13 for Age Cohort 1 and n=15 for Age Cohort 2) and all concentrations were reported as below the limit of quantitation (BLQ, <5.00 ng/mL).
[a] For n < 3, individual plasma concentration values were presented, separated by a comma. Otherwise, plasma concentrations were presented as GM (GCV%) [n].

Table 8: Summary of POS 3 to 6h post oral dose (up) or 15 mn after IV (down), by Age cohort and by formulation

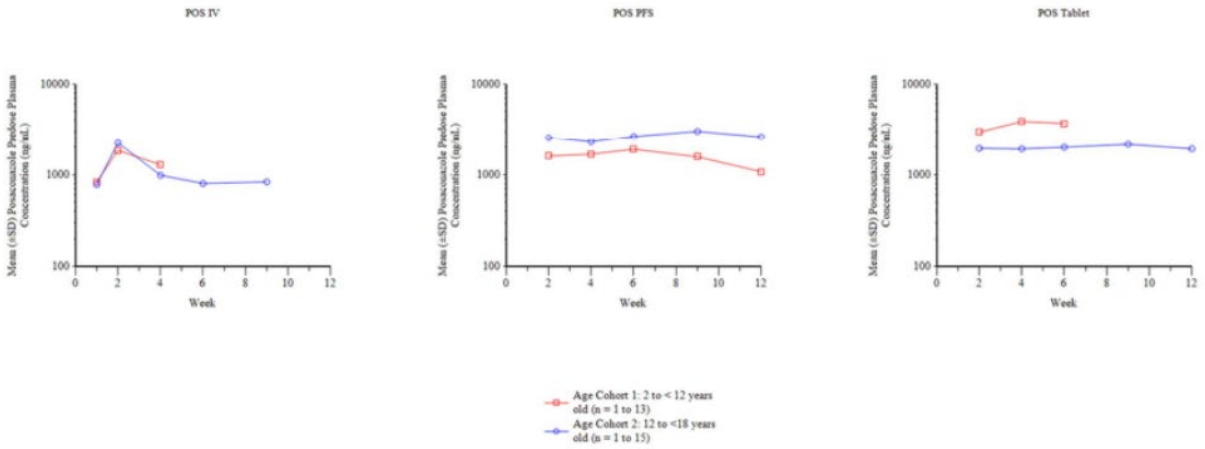
		Visit				
		Week 2	Week 4	Week 6	Week 9	Week 12
		POS Plasma Concentration 3 to 6 Hours Post Oral Dose (ng/mL)				
Age Cohort	Formulation	GM (GCV%) [n][a]				
1 (2 to < 12 years old)	POS PFS	2194 (30.2) [4]	2261, 2731	1783, 2302	2612	1019
2 (12 to <18 years old)	POS PFS	3741	2694, 3694	2419, 4820	3115, 5992	3045
	POS Tablet	2076 (80.5) [6]	7914	2122 (44.5) [5]	2199 (32.0) [4]	1957 (103.2) [5]

GCV = geometric coefficient of variation; GM = geometric mean; n = number of observations; NC = not calculated; PFS = Powder for suspension; POS = Posaconazole.
[a] For n < 3, individual plasma concentration values were presented, separated by a comma. Otherwise, plasma concentrations were presented as GM (GCV%) [n].

		Visit				
		Week 1	Week 2	Week 4	Week 6	Week 9
		POS Plasma Concentration 15 Minutes Post IV Infusion (ng/mL)				
Age Cohort	Formulation	GM (GCV%) [n][a]				
1 (2 to < 12 years old)	POS IV	3354 (43.9) [9]	3746 (42.8) [5]	2923, 3163	NC	NC
2 (12 to <18 years old)	POS IV	4397 (73.7) [13]	3231 (66.7) [6]	2649 (20.2) [3]	2232	1789

GCV = geometric coefficient of variation; GM = geometric mean; IV = Intravenous; n = number of observations; NC = not calculated; PFS = Powder for suspension; POS = Posaconazole.
[a] For n < 3, individual plasma concentration values were presented, separated by a comma. Otherwise, plasma concentrations were presented as GM (GCV%) [n].

Figure 1: Mean pre-dose (trough) plasma concentration vs time of POS by Age cohort and formulation



Based on the PPK analysis, Table 9 presents the predicted exposure metrics in study P104.

Table 9: Paediatric summary of model-predicted steady-state PK parameters for POS following respective protocol dosing regimen

Parameter	Age Group	Formulation	m[b]	Mean (SD)	%CV	Geometric Mean (%geoCV)	Minimum	Median	Maximum
AUCtau (ng•h/mL)	≥2 to <12 years	IV	9	67600 (27500)	40.6	61900 (49.8)	25700	64500	110000
		PFS	6	46800 (13200)	28.2	45200 (30.2)	28200	47100	67000
		Tablet	1	NR	NR	NR	90600	NR	90600
	≥12 to <18 years	IV	13	64100 (21200)	33.0	60800 (35.6)	29900	63700	106000
		PFS	2	NR	NR	NR	66400	NR	97000
		Tablet	10	52900 (23300)	44.0	47800 (52.7)	20400	51800	85000
Cavg (ng/mL)	≥2 to <12 years	IV	9	2820 (1140)	40.6	2580 (49.8)	1070	2690	4600
		PFS	6	1950 (550)	28.2	1880 (30.2)	1170	1960	2790
		Tablet	1	NR	NR	NR	3780	NR	3780
	≥12 to <18 years	IV	13	2670 (883)	33.0	2530 (35.6)	1250	2650	4420
		PFS	2	NR	NR	NR	2770	NR	4040
		Tablet	10	2210 (971)	44.0	1990 (52.7)	848	2160	3540
Cmax (ng/mL)	≥2 to <12 years	IV	9	3770 (1070)	28.5	3630 (30.8)	2170	3720	5500
		PFS	6	2280 (578)	25.3	2220 (26.5)	1530	2260	3080
		Tablet	1	NR	NR	NR	4120	NR	4120
	≥12 to <18 years	IV	13	3620 (901)	24.9	3510 (26.8)	1950	3480	5300
		PFS	2	NR	NR	NR	3130	NR	4370
		Tablet	10	2460 (1010)	41.0	2250 (48.3)	1040	2490	3800

Parameter	Age Group	Formulation	m[b]	Mean (SD)	%CV	Geometric Mean (%geoCV)	Minimum	Median	Maximum
Cmin (ng/mL)	≥2 to <12 years	IV	9	2060 (1110)	54.0	1710 (82.2)	410	1860	3800
		PFS	6	1450 (531)	36.6	1370 (41.8)	677	1420	2330
		Tablet	1	NR	NR	NR	3220	NR	3220
	≥12 to <18 years	IV	13	1910 (841)	44.1	1740 (48.5)	727	1800	3640
		PFS	2	NR	NR	NR	2200	NR	3500
		Tablet	10	1810 (906)	50.1	1580 (62.6)	570	1650	3110
Tmax (h)	≥2 to <12 years	IV	9	NA	NA	NA	1.25	1.50	1.77
		PFS	6	NA	NA	NA	6.40	7.00	7.20
		Tablet	1	NA	NA	NA	7.30	NR	7.30
	≥12 to <18 years	IV	13	NA	NA	NA	1.30	1.50	1.63
		PFS	2	NA	NA	NA	7.10	NR	7.30
		Tablet	10	NA	NA	NA	6.70	7.15	7.30

The CHMP considered that, although the PK study design was acceptable, information on the planned PK sampling protocol was unclear. Based on the raw PK data submitted as part of this application, the PK sampling can be described as follows:

- IV formulation: pre-dose at Day 1, week 1, 2 and 4, 15min- post infusion at weeks 1, 2 and 4
- PFS and Tablet: pre-dose and post-dose (3 to 6h) at weeks 2, 4, 6, 9 and 12.

The CHMP noted that seemingly one subject in cohort 1 received the tablet formulation with unexpected Ctrough approximately twice higher than those observed in this cohort (2904-3706 ng/mL vs 1433- 1734 ng/mL). In cohort 2, two subjects received the PFS formulation with Ctrough numerically higher than those receiving the tablet formulation. However, except these 3 subjects, if the observed geomean Ctrough between Cohort 1 and Cohort 2 for the IV formulation and for the PFS (cohort 1) vs Tablet (cohort 2) formulation are compared, similar results are observed, which is reassuring, and all are well above the 500 ng/mL threshold (Cavg target used for a previous application).

2.3.5. Population PK analysis

Objectives

The objectives of the analysis were to:

- Perform an external validation of the existing paediatric prophylaxis PPK model based on the newly available paediatric PK data from studies P104 and P127 and update the PPK model
- Re-assess the impact of covariates on POS PK in paediatric patients
- Generate EBE of individual exposure estimates for participants from study P104
- Explore ER for preselected efficacy and safety endpoints based on study P104
- Conduct simulations of POS exposure in paediatric population to support PK exposure comparisons between various paediatric sub-groups aged 2 to 18 years and adults and between indication (IFI prophylaxis vs IA)

The CHMP noted that, as part of a previous Noxafil procedure (EMEA/H/C/000610/X/0063/G), the MAH had developed a PPK model based on PK data from study P097. Study P097 was a 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. At that time, 118 subjects between 2-<18 years were enrolled and divided in two groups (2 to <7 years and 7 to <18 years). No concerns were raised with regards to this previous PPK model.

2.3.6. PK/PD modelling

Methods

The PPK of POS was based on PK results pooling 3 clinical studies performed in paediatric participants (P097, P104 and P127). The concentration-time data of POS was modelled using a compartmental approach. PK data were log-transformed.

Covariates of interest in POS trials were baseline demographics (gender, age and body weight), race and disease status.

PPK was built using non-linear mixed effects model with the first order conditional with interaction (FOCEI) for parameter estimation implemented in NONMEM (version 7.5.1, ICON, Hanover, MD, US). Except body weight (BW) as used as part of the structural PK mode using allometric scaling (fixed coefficient to the theoretical values then estimated), the other covariates were tested using a stepwise/backward selection procedure. Then the PopPK model was evaluated using standard goodness of fit plots, bootstrap and pcVPCs.

For each individual, based on EBE, steady-state Cavg were derived based following IV or oral formulation administration using Cavg=(Dose/CL)/24 or Cavg=(Dose/[CL/F])/24, respectively. Other PK parameters were also predicted as Cmax, AUC and Ctrough. Theses predicted PK parameters were used for ER analysis.

In addition, the final PPK model was used to simulate the distribution of POS exposure in virtual patients under various age (1000 virtual subjects aged 6 months-<2 years, 2-<7 years, 7 to <12 years, 12 to < 18 years) and BW groups (5 to 155 kg) in order to derive the following metrics:

- percent of the population achieving exposure range Cavg≥500 ng/mL, this was considered the primary concentration target associated with POS efficacy
- percent of the population achieving exposure range Cmin≥500 ng/mL and Cavg≥700 ng/mL, this was considered the secondary concentration targets for efficacy

Finally, the following proportions were calculated:

- Cavg< 500 ng/mL and Cavg≥500 ng/mL or Cavg < 700 ng/mL and Cavg≥700 ng/mL
- 500 ≤ Cavg ≤ 2500 ng/mL or 700 ≤ Cavg ≤ 2500 ng/mL
- Cavg ≥2500 ng/mL

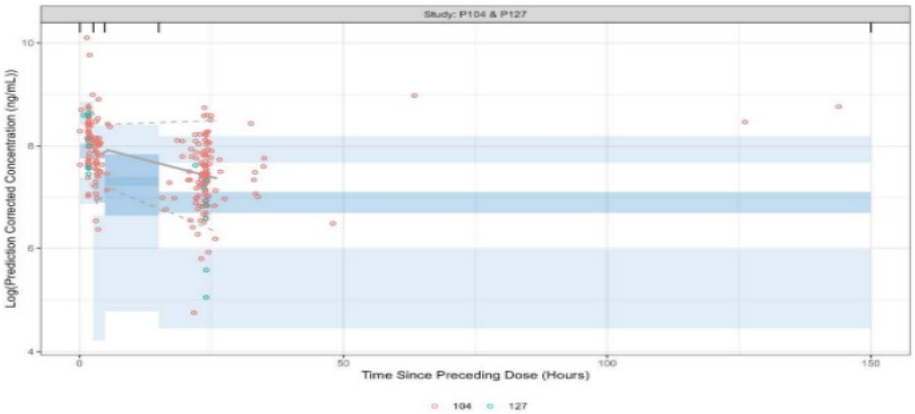
Of note, the reference adult population targets were derived by simulation using PK data from adult studies (P069, P05615, P101, P117, P120 and P05520).

Results

- External model validation

Using the existing PPK model based on PK data from study 097, an external validation step was first performed to check if this PPK model was able to adequately describe the PK data from studies P107 and P124 using a pcVPC. Results are presented in Figure 2 and clearly show that the PPK model need to be updated.

Figure 2: pcVPC of the external validation model for studies P104 and P127



- New PPK model

PK dataset

The combined PPK analysis dataset from studies P097, P104 and P127 consisted of 153 participants and 1505 POS observations. In total 114 participants and 1243 observations originated from study P097 (PFS and IV formulations), 31 participants and 238 observations originated from study P104 (PFS, tablet and IV formulations) and 8 participants and 24 observations from study P127 (IV only). From study P104 and P127, 37 pre-dose BQL samples were excluded, one subject from study P104 had non evaluable PK data and 2 observations were considered outliers. In total, the PK dataset consisted of 1391 PK data from 149 subjects.

Table 10: Summary of POS PK observations

Study	Total N	N Final Model	Obs. (%) Final Model	N non-eval.	Obs. (%) Predose BLQs	Obs. (%) Postdose BLQs	Obs. (%) Excluded from P097 Model	Outl. Flagged in P097	Err. TSFD Value	Incompl. Dose	Outl. (%) Final Model	Outl. (%) Low F	Total Obs.
P097	114	112	1169 (94.05)	0 (0)	0 (0)	6 (0.48)	12 (0.97)	4 (0.32)	5 (0.4)	33 (2.65)	1 (0.08)	13 (1.05)	1243
P104	31	29	206 (86.55)	1 (0.42)	29 (12.18)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.84)	0 (0)	238
P127	8	8	16 (66.67)	0 (0)	8 (33.33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	24

Figure 3 presents a plot of the observed PK data split by age. Figure 4 presents the dose-normalized POS plasma concentration split by formulation and categorized by study, Table 10 the summary of the number of subjects per formulations and Table 11 the summary statistics of the categorical and continuous potential covariates.

Figure 3: POS plasma concentration-time plots by age group

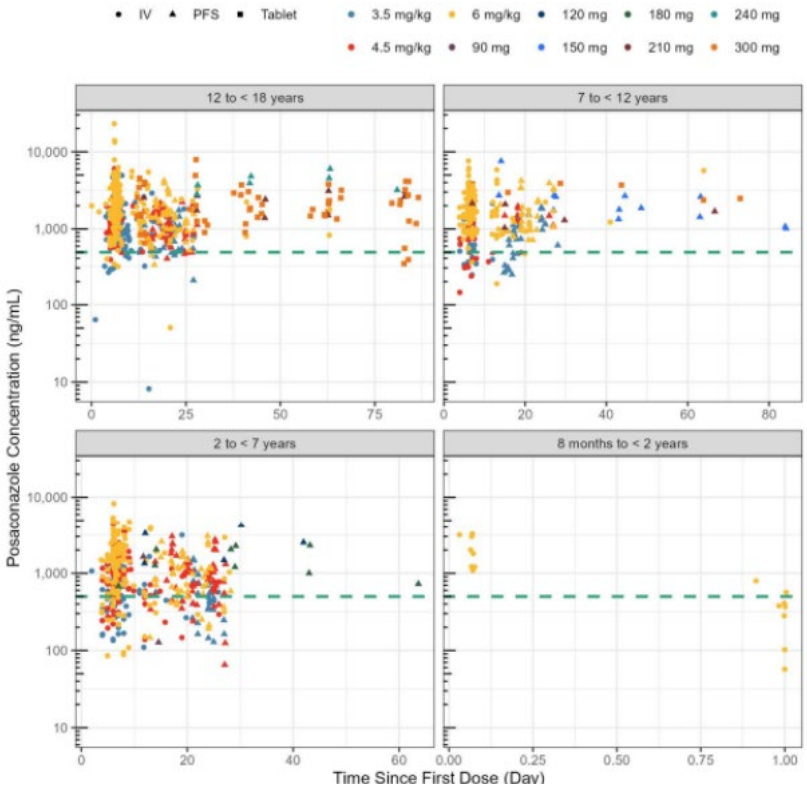


Figure 4: Dose-normalized POs plasma concentration-time plots by formulation and categorized by study

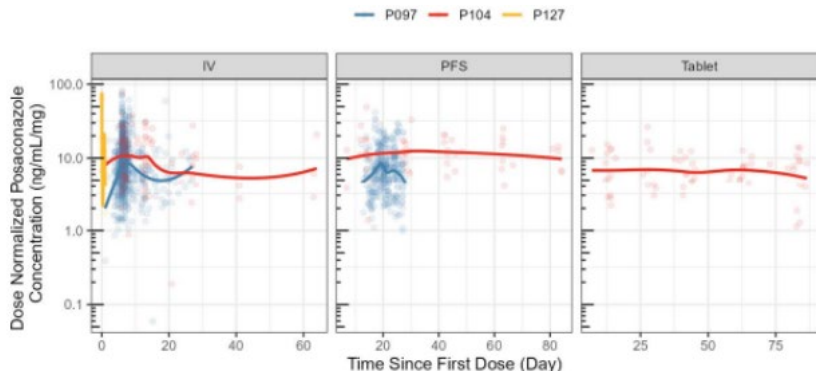


Table 11: Summary of nominal dose by study and formulation in the PPK analysis

Nominal Dose	P097		P104			P127	Overall		
	IV (N=112)	PFS (N=58)	IV (N=27)	PFS (N=10)	Tablet (N=11)	IV (N=8)	IV (N=147)	PFS (N=68)	Tablet (N=11)
3.5 mg/kg	34 (30%)	15 (26%)	NA	NA	NA	NA	34 (23%)	15 (22%)	NA
4.5 mg/kg	30 (27%)	17 (29%)	NA	NA	NA	NA	30 (20%)	17 (25%)	NA
6 mg/kg	48 (43%)	26 (45%)	27 (100%)	NA	NA	8 (100%)	83 (56%)	26 (38%)	NA
90 mg	NA	NA	NA	1 (10%)	NA	NA	NA	1 (1%)	NA
120 mg	NA	NA	NA	2 (20%)	NA	NA	NA	2 (3%)	NA
150 mg	NA	NA	NA	3 (30%)	NA	NA	NA	3 (4%)	NA
180 mg	NA	NA	NA	1 (10%)	NA	NA	NA	1 (1%)	NA
210 mg	NA	NA	NA	2 (20%)	NA	NA	NA	2 (3%)	NA
240 mg	NA	NA	NA	1 (10%)	NA	NA	NA	1 (1%)	NA
300 mg	NA	NA	NA	NA	11 (100%)	NA	NA	NA	11 (100%)

Table 12: Summary of continuous and categorical covariates

	P097 (N=112)	P104 (N=29)	P127 (N=8)	Overall (N=149)
Age (years)				
Mean (SD)	8.95 (4.96)	11.3 (4.26)	1.36 (0.498)	8.99 (5.11)
Median [min, max]	8.50 [2.00, 17.0]	12.0 [2.00, 17.0]	1.36 [0.690, 1.99]	9.00 [0.690, 17.0]
Weight (kg)				
Mean (SD)	36.0 (22.3)	39.7 (14.6)	9.64 (2.78)	35.3 (21.3)
Median [min, max]	28.6 [10.2, 102]	44.7 [12.3, 65.5]	10.1 [5.50, 14.2]	29.5 [5.50, 102]
Body mass index (kg/m^2)				
Mean (SD)	18.1 (4.67)	18.0 (3.37)	15.0 (2.25)	17.9 (4.38)
Median [min, max]	16.5 [12.6, 33.7]	17.3 [13.6, 24.9]	14.8 [11.2, 18.5]	16.5 [11.2, 33.7]
Missing	2 (1.8%)	0 (0%)	0 (0%)	2 (1.3%)
Body surface area (m^2)				
Mean (SD)	1.14 (0.474)	1.27 (0.337)	0.447 (0.0854)	1.13 (0.468)
Median [min, max]	1.02 [0.475, 2.26]	1.33 [0.541, 1.78]	0.458 [0.323, 0.589]	1.05 [0.323, 2.26]
Missing	2 (1.8%)	0 (0%)	0 (0%)	2 (1.3%)

	P097 (N=112)	P104 (N=29)	P127 (N=8)	Overall (N=149)
IFI intervention, N (%)				
Prophylaxis	112 (100%)	0 (0%)	0 (0%)	112 (75.2%)
Treatment	0 (0%)	29 (100%)	8 (100%)	37 (24.8%)
Age group, N (%)				
12 to <18 years	43 (38.4%)	16 (55.2%)	0 (0%)	59 (39.6%)
7 to <12 years	22 (19.6%)	8 (27.6%)	0 (0%)	30 (20.1%)
2 to <7 years	47 (42.0%)	5 (17.2%)	0 (0%)	52 (34.9%)
8 months to <2 years	0 (0%)	0 (0%)	8 (100%)	8 (5.4%)
Weight group, N (%)				
5 to <10 kg	0 (0%)	0 (0%)	4 (50.0%)	4 (2.7%)
10 to <15 kg	18 (16.1%)	2 (6.9%)	4 (50.0%)	24 (16.1%)
15 to <20 kg	16 (14.3%)	1 (3.4%)	0 (0%)	17 (11.4%)
20 to <25 kg	20 (17.9%)	3 (10.3%)	0 (0%)	23 (15.4%)
25 to <30 kg	4 (3.6%)	3 (10.3%)	0 (0%)	7 (4.7%)
30 to <40 kg	13 (11.6%)	4 (13.8%)	0 (0%)	17 (11.4%)
40 to <50 kg	13 (11.6%)	8 (27.6%)	0 (0%)	21 (14.1%)
50 to <60 kg	10 (8.9%)	6 (20.7%)	0 (0%)	16 (10.7%)
60 to <70 kg	7 (6.3%)	2 (6.9%)	0 (0%)	9 (6.0%)
≥70 kg	11 (9.8%)	0 (0%)	0 (0%)	11 (7.4%)
Sex, N (%)				
Male	66 (58.9%)	22 (75.9%)	5 (62.5%)	93 (62.4%)
Female	46 (41.1%)	7 (24.1%)	3 (37.5%)	56 (37.6%)
Race, N (%)				
White	94 (83.9%)	15 (51.7%)	6 (75.0%)	115 (77.2%)
Black or African American	3 (2.7%)	0 (0%)	2 (25.0%)	5 (3.4%)
Asian	10 (8.9%)	8 (27.6%)	0 (0%)	18 (12.1%)
Multiracial	4 (3.6%)	6 (20.7%)	0 (0%)	10 (6.7%)
Native Hawaiian	1 (0.9%)	0 (0%)	0 (0%)	1 (0.7%)
Ethnicity, N (%)				
Hispanic or Latino	12 (10.7%)	7 (24.1%)	0 (0%)	19 (12.8%)
Not Hispanic or Latino	97 (86.6%)	22 (75.9%)	8 (100%)	127 (85.2%)
Missing	3 (2.7%)	0 (0%)	0 (0%)	3 (2.0%)

Final PPK model

From the previous PPK model, the omega block between CL and V was removed and a treatment effect (disease status) was added on CL, and the exponents of the allometric scaling were estimated instead of being fixed, run 2009 was therefore selected as the final PPK model (Table 13).

Table 13: Summary model development and refinement

Model Number	Reference Model	Description	OFV	dOFV
Run2001	NA	Previous final pediatric model – updated dataset	-986.03	NA
Run2002	run2001	MAXEVAL=0; excluding outliers based on run2001	-1035.94	NA
Run2003	run2002	Estimate parameters	-1043.62	-7.68
Run2004	run2003	Excluding 2 participants with low bioavailability (oral data only)	-1090.04	NA
Run2005	run2004	Excluding outliers based on |CWRES|>6	-1136.13	NA
Run2006	run2005	Update median body weight	-1136.13	0.00
Run2007	run2006	Fix tablet bioavailability to adult value	-1135.62	0.50
Run2008	run2007	Remove OMEGA BLOCK prior to SCM	-1119.66	15.96

Model Number	Reference Model	Description	OFV	dOFV
Run2008	run2007	Remove OMEGA BLOCK prior to SCM	-1119.66	15.96
Run2009	run2008	Final model from SCM; TREAT effect on CL	-1130.66	-11.00
Run2010	run2009	OMEGA BLOCK CL and V	-1143.17	-12.51
Run2020	run2008	Fix AS exponents to standards values 0.75 and 1	-1110.56	9.10
Run2021	run2009	TREAT effect on CL; fix AS exponents to standard values 0.75 and 1	-1119.72	10.95

The final PPK model parameter estimates are provided in Table 14, associated GOF plots in Figure 5 and pcVPC plots in Figure 6 for all the data and for studies P104 and P127.

Table 14: Final PPK model of POS in the paediatric population

Parameter	Value	%RSE	Shrinkage (%)
CL (L/hr)	4.36	3.7	NA
V (L)	99.8	4.8	NA
Ka (h^{-1})	0.215	16.4	NA
F - PFS	0.849	4.4	NA
F - tablet	0.819 Fixed	NA	NA
Allometric exponent of CL	0.582	8.8	NA
Allometric exponent of V	1.02	7.1	NA
Participants with IFI - CL	-0.227	26.0	NA
IIV CL (%CV)	37.3	6.6	6.5
IIV V (%CV)	24.2	34.0	44.7
IIV F (SD)	2.19	29.2	46.6
Residual error (SD)	0.330	4.1	NA

Figure 5: Log-log standard GOF diagnostic plots from the final POS model

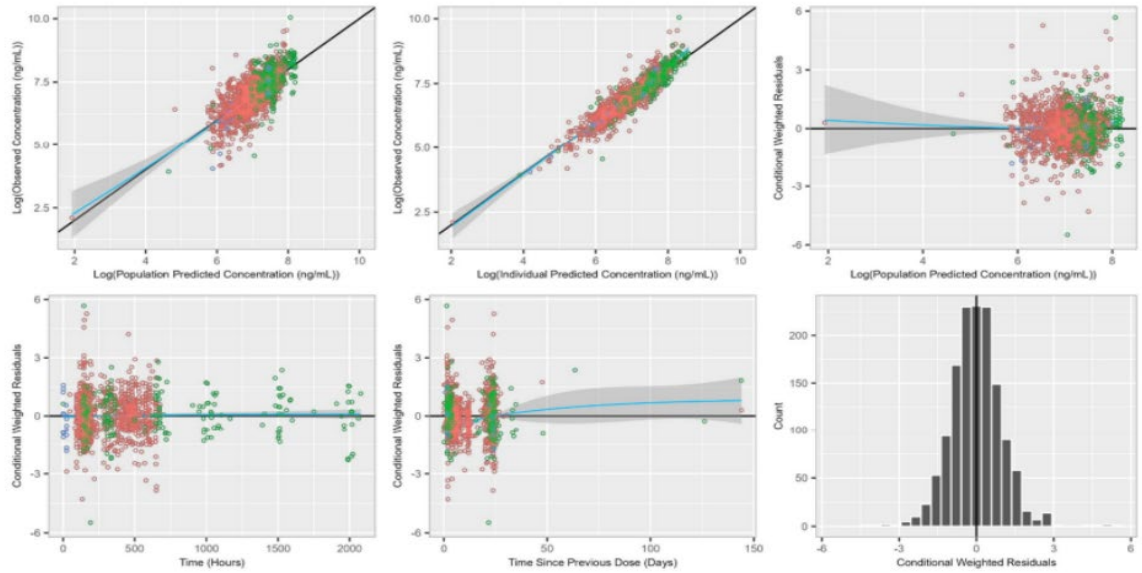
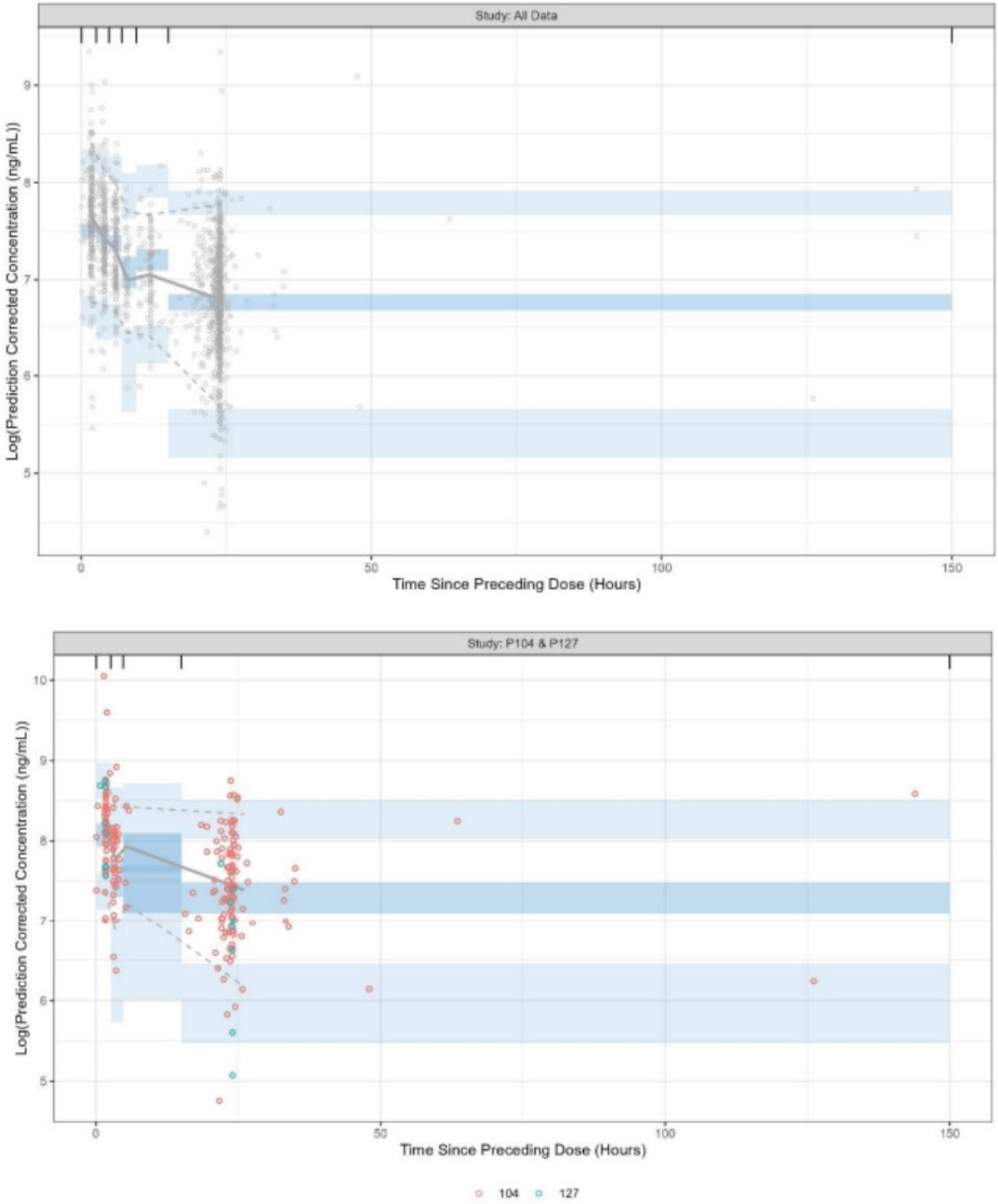


Figure 6: pcVPC from the final POS model for all data (up) and for study P104 and P127 (down)



With regards to the PPK model, the CHMP noted that the PPK model was based on a large cohort of paediatric subjects across three studies with age ranging from 8 months to 17 years, with BW from 5.5 to 102 kg (for P104, BW: 12-65 kg).

Although the MAH claimed that a total of 149 subjects with n=1391 PK observations were considered, the control stream indicated 150 subjects with 1391 observations (Run 2008). From the initial PK dataset to the final, for Study 104, 29 BQL pre-dose were discarded, which was acceptable. One observation was flagged as non-evaluable and 2 were considered outliers.

The PPK model shared the same structure as previously described for study P097 and consisted of a compartmental (cpt) model parameterized in terms of CL, Vc, ka and F (bioavailability, logit function). BW allometric scaling with estimated exponents (0.582 for CL and 1.02 for Vc). F-PFS was estimated at 0.849 and F tablet fixed to 0.819 (please refer to EMEA/H/C/000610/II/0062). Ka was fixed, CL and Vc estimated at 4.36 L/h and 99.8 L respectively with moderate IIV 37.3 and 24.2% with low and high shrinkage respectively (6.5 and 44.7%). IIV for F was particularly high with an IIV of 148%.

A disease status effect was identified as a significant covariate for CL, where participant treated for IA demonstrated a 22.7% lower CL compared to subjects at risk of IFI. The disease status effect has been previously described in EMEA/H/C/000610/II/0062 where in adults treated for an IA compared to healthy volunteers a 11% decreased of CL was observed and in adults treated for another infection compared to healthy volunteers a 43.7% decreased for CL was observed. The MAH attributed this difference to the underlying physical conditions and disease severity between prophylaxis and treated patients. And this difference contributed to the altered disposition of POS, which was considered plausible and acceptable by the CHMP.

Overall PK parameters were estimated with good precision, GOF does not show a particular bias and pcVPC shows reasonably adequate predictive performance.

- Cmax and Ctrough, Observed vs predicted

The CHMP considered that the comparisons between the predicted Cmax and Cmin by the PPK model with the observed Cmax and Ctrough for the IV and oral formulations, indicate similar results, confirming the adequacy of the developed PPK model.

- Simulations

The simulated POS dosing regimen in paediatric patients aged 2 to < 18 years is presented in Table 15.

Table 15: Proposed POS dosing regimen in paediatric patients for treatment of IA and IFI prophylaxis

Route	Formulation	Dose Strength	≤10 kg	10 to <12 kg	12 to <17 kg	17 to <21 kg	21 to <26 kg	26 to <36 kg	36 to <40 kg	≥40 kg
IV	IV	18 mg/mL	6 mg/kg (up to 300 mg) BID on Day 1 followed by 6 mg/kg QD over a 90-min infusion							
Oral[a]	PFS	30 mg/mL	NA	90 mg (3 mL)	120 mg (4 mL)	150 mg (5 mL)	180 mg (6 mL)	210 mg (7 mL)	240 mg (8 mL)	NA
	Tablet	100 mg	NA							300 mg BID on Day 1 followed by 300 mg QD

Summary statistics of predicted POS exposures Cavg and Cmin by age group, formulation and intervention type are summarized in Table 16 and per weight group in Table 17, both compared to the adult reference population. The associated boxplots are presented in Figure 7 and Figure 8. Table 15 presents the proportion of patients achieving the specific ranges of simulated POS Cavg and Cmin and per weight group for the IA treatment.

For Cavg, the primary exposure metric associated with POS efficacy, nearly all simulated patients (approaching 100%) are predicted to achieve Cavg ≥500 ng/mL when treated with the IV formulation, regardless of paediatric age groups or intervention types. This finding is consistent with the predictions in adult populations. For both PFS and tablet, in each of the paediatric age groups across both intervention types, the proportion of simulated patients with Cavg ≥500 ng/mL remains

above 90%. Similar conclusions can be drawn across different paediatric proposed weight bands and for all 3 formulations for the treatment of IA.

Table 16: Predicted geometric mean Cavg and Cmin at the proposed dosing regimen for treatment of IA and IFI prophylaxis per age group in virtual paediatric patients aged ≥ 2 years

Intervention	Parameter	Formulation	2 to <7 Years			7 to <12 Years			12 to <18 Years			Adult		
			N	Geometric Mean (ng/mL)	Geometric CV (%)	N	Geometric Mean (ng/mL)	Geometric CV (%)	N	Geometric Mean (ng/mL)	Geometric CV (%)	N	Geometric Mean (ng/mL)	Geometric CV (%)
Treatment	Cavg	IV	1000	1820	40	1000	2270	38	1000	2360	39.7	124	2100	49.6
		PFS	988	1780	59.3	671	1840	58.7	47	1980	44.2	NA	NA	NA
		Tablet	9	2170	46.6	329	1830	65.9	953	1690	58.7	224	2220	42.3
	Cmin	IV	1000	1020	72.5	1000	1490	59.1	1000	1690	53.5	124	1740	59.1
		PFS	988	1230	76.1	671	1370	69.9	47	1500	54.5	NA	NA	NA
		Tablet	9	1700	50.1	329	1450	74.2	953	1370	65.8	224	1960	47.4
Prophylaxis	Cavg	IV	1000	1370	38.9	1000	1780	38.5	1000	1820	41.1	NA	NA	NA
		PFS	988	1380	53.6	671	1420	56.4	47	1420	51.5	NA	NA	NA
		Tablet	9	1690	59.1	329	1420	59.8	953	1320	63.7	230	1870	45.5
	Cmin	IV	1000	623	87.9	1000	1020	69.9	1000	1180	59.9	NA	NA	NA
		PFS	988	828	77.4	671	957	72.7	47	1010	59.8	NA	NA	NA
		Tablet	9	1160	71.2	329	1050	70	953	1000	73.5	230	1640	51.9

Table 17: Predicted geometric mean Cavg and Cmin at the proposed dosing regimen for treatment of IA per weight group in virtual paediatric patients aged ≥ 2 years

Weight Category	IV-Pediatrics			IV-Adults			PFS-Pediatrics			Tablet-Pediatrics			Tablet-Adults		
	N	Geometric Mean (ng/mL)	Geometric CV (%)	N	Geometric Mean (ng/mL)	Geometric CV (%)	N	Geometric Mean (ng/mL)	Geometric CV (%)	N	Geometric Mean (ng/mL)	Geometric CV (%)	N	Geometric Mean (ng/mL)	Geometric CV (%)
4 to <10 kg	3	1380	39.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
10 to <12 kg	38	1420	33.9	NA	NA	NA	38	1290	57.2	NA	NA	NA	NA	NA	NA
12 to <17 kg	398	1650	38.2	NA	NA	NA	398	1670	62.5	NA	NA	NA	NA	NA	NA
17 to <21 kg	318	1860	38.3	NA	NA	NA	318	1820	60.1	NA	NA	NA	NA	NA	NA
21 to <26 kg	335	2050	37.1	NA	NA	NA	335	1910	61	NA	NA	NA	NA	NA	NA
26 to <36 kg	482	2200	36.4	NA	NA	NA	482	1890	51.2	NA	NA	NA	NA	NA	NA
36 to <40 kg	135	2350	35.8	2	2790	11.4	135	1870	58.1	NA	NA	NA	1	2570	NA
40 to <50 kg	367	2680	38.2	12	2310	50.6	NA	NA	NA	367	2010	63.4	22	2630	43.2
50 to <70 kg	611	2460	35.8	61	2330	49.5	NA	NA	NA	611	1730	57.2	99	2340	43.4
70 to <90 kg	216	2130	42.5	39	1790	48.8	NA	NA	NA	216	1480	61.6	83	2040	39
90 to <110 kg	56	1860	38.5	8	1780	34.8	NA	NA	NA	56	1490	45.8	17	1880	41.8
≥110 kg	41	1660	34.5	2	1730	51.3	NA	NA	NA	41	1210	44.7	2	2620	9.97

Figure 7: Distribution of simulated POS Cavg per weigh group based on the proposed oral dosage regimen compared to adult participants treated for IA

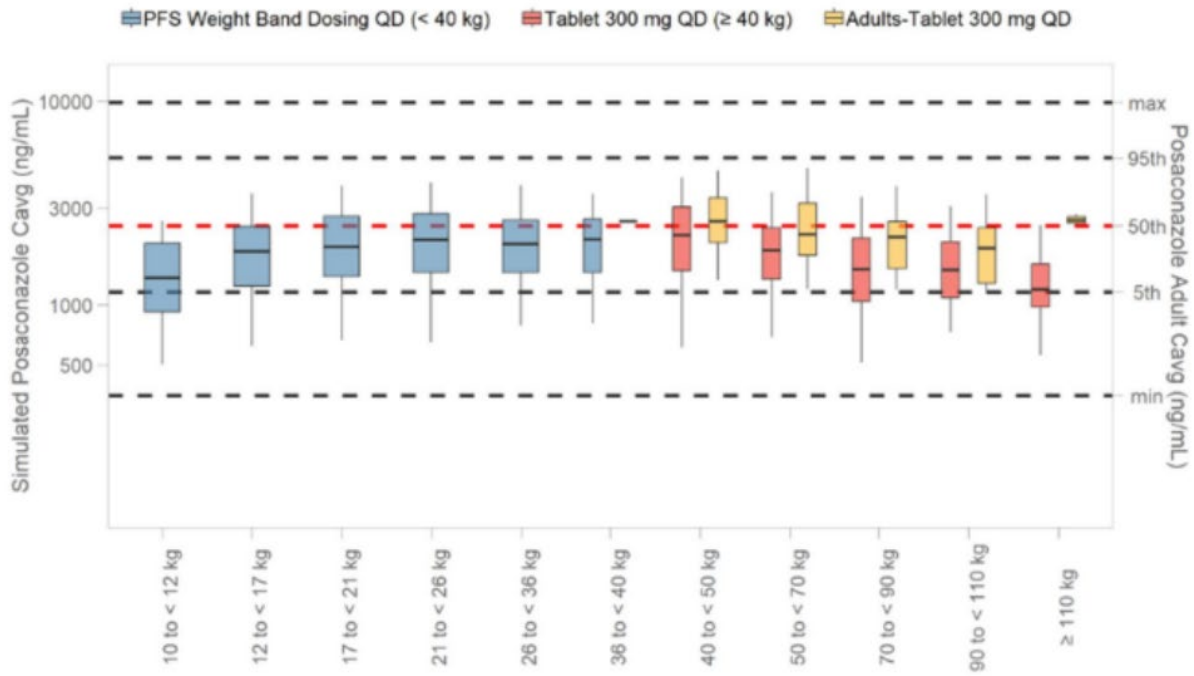


Figure 8: Distribution of simulated POS Cavg per weigh group based on the proposed IV dosage regimen compared to adult participants treated for IA

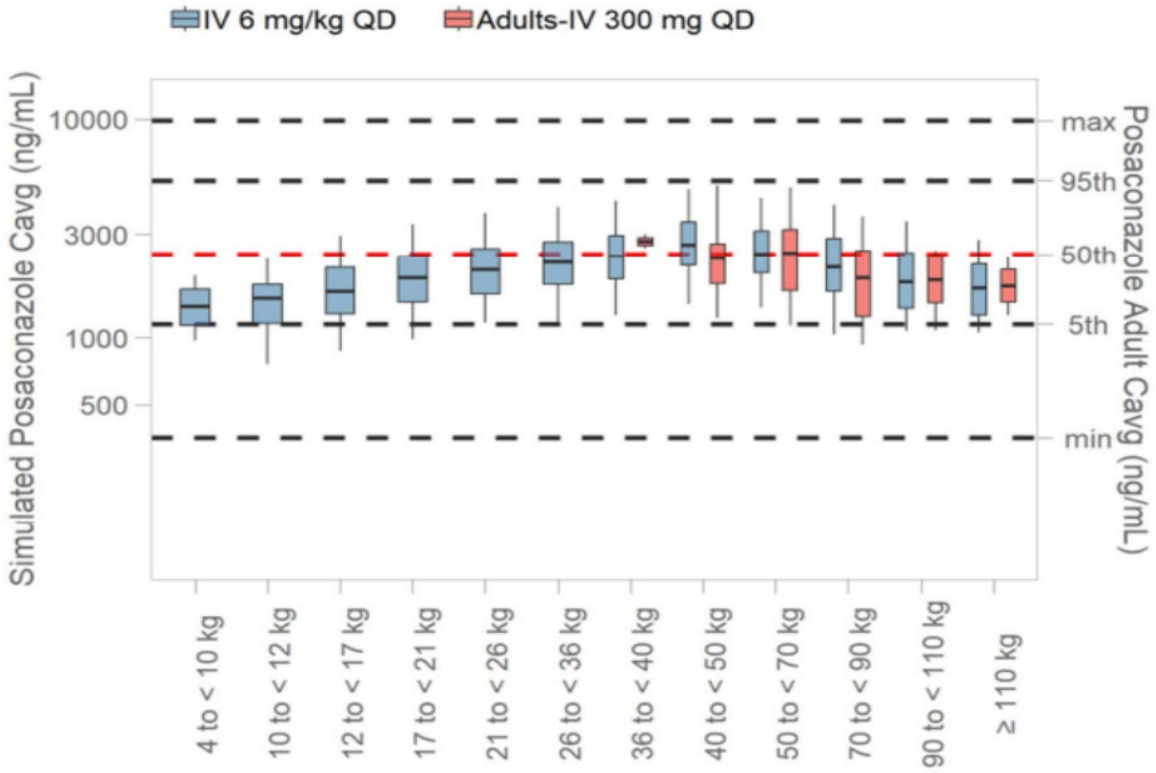


Table 18: Proportions of patients achieving the specific ranges per age (up) and weight group (down) for treatment of IA (up and down) or IFI prophylaxis (up).

Intervention	Parameter	Formulation	2 to <7 Years				7 to <12 Years				12 to <18 Years				Adult			
			N	<500 ng/mL	≥500 to <2500 ng/mL	≥2500 ng/mL	N	<500 ng/mL	≥500 to <2500 ng/mL	≥2500 ng/mL	N	<500 ng/mL	≥500 to <2500 ng/mL	≥2500 ng/mL	N	<500 ng/mL	≥500 to <2500 ng/mL	≥2500 ng/mL
Treatment	Cavg	IV	1000	0	80.3	19.7	1000	0	59	41	1000	0	56.3	43.7	124	0	62.9	37.1
		PFS	988	2.63	70	27.3	671	2.24	68.4	29.4	47	0	66	34	0	0	0	0
		Tablet	9	0	66.7	33.3	329	3.34	65	31.6	953	2.52	74	23.5	224	0	61.2	38.8
	Cmin	IV	1000	12.7	80.3	7	1000	3.8	80	16.2	1000	1.8	75.7	22.5	124	3.23	71	25
		PFS	988	9.72	77.7	12.6	671	6.41	79.3	14.3	47	2.13	87.2	10.6	0	0	0	0
		Tablet	9	0	77.8	22.2	329	8.21	72.3	19.5	953	5.67	78.8	15.5	224	0.446	71.4	28.1
Prophylaxis	Cavg	IV	1000	0.2	94.7	5.1	1000	0	82.5	17.5	1000	0.1	77.4	22.5	0	0	0	0
		PFS	988	3.95	87.3	8.7	671	3.73	83.9	12.4	47	2.13	91.5	6.38	0	0	0	0
		Tablet	9	0	77.8	22.2	329	4.26	82.4	13.4	953	4.83	84.3	10.9	230	0.435	76.1	23.5
	Cmin	IV	1000	33.5	65.5	1	1000	12.3	81.7	6	1000	6.9	85.8	7.3	0	0	0	0
		PFS	988	21.9	75.2	2.94	671	14.5	80.2	5.37	47	10.6	87.2	2.13	0	0	0	0
		Tablet	9	11.1	66.7	22.2	329	10.6	82.1	7.29	953	13	81.3	5.67	230	3.04	79.1	16.1

Weight Categories	IV-Pediatric			IV-Adults (P069)			PFS-Pediatric				Tablet-Pediatric				Tablet-Adults (P069)		
	N	≥500 to <2500 ng/mL	≥2500 ng/mL	N	≥500 to <2500 ng/mL	≥2500 ng/mL	N	<500 ng/mL	≥500 to <2500 ng/mL	≥2500 ng/mL	N	<500 ng/mL	≥500 to <2500 ng/mL	≥2500 ng/mL	N	≥500 to <2500 ng/mL	≥2500 ng/mL
4 to <10 kg	3	100	0	0	0	0	0	0	0	0	NA	NA	NA	NA	0	0	0
10 to <12 kg	38	100	0	0	0	0	38	5.26	86.8	7.89	NA	NA	NA	NA	0	0	0
12 to <17 kg	398	87.9	12.1	0	0	0	398	3.27	73.6	23.1	NA	NA	NA	NA	0	0	0
17 to <21 kg	318	76.4	23.6	0	0	0	318	1.89	68.9	29.2	NA	NA	NA	NA	0	0	0
21 to <26 kg	335	72.2	27.8	0	0	0	335	2.99	63.6	33.4	NA	NA	NA	NA	0	0	0
26 to <36 kg	482	63.5	36.5	0	0	0	482	1.45	68.9	29.7	NA	NA	NA	NA	0	0	0
36 to <40 kg	135	54.8	45.2	2	0	100	135	2.22	68.1	29.6	NA	NA	NA	NA	1	0	100
40 to <50 kg	367	40.3	59.7	12	66.7	33.3	NA	NA	NA	NA	367	1.63	58.6	39.8	22	40.9	59.1
50 to <70 kg	611	53.5	46.5	61	54.1	45.9	NA	NA	NA	NA	611	2.78	74.8	22.4	99	58.6	41.4
70 to <90 kg	216	68.5	31.5	39	71.8	28.2	NA	NA	NA	NA	216	5.09	77.8	17.1	83	67.5	32.5
90 to <110 kg	56	75	25	8	87.5	12.5	NA	NA	NA	NA	56	0	83.9	16.1	17	76.5	23.5
≥110 kg	41	85.4	14.6	2	100	0	NA	NA	NA	NA	41	2.44	92.7	4.88	2	50	50

The CHMP noted that a thorough simulation exercise was performed, allowing the comparison of predicted exposure POS (Cavg and Cmin) across indications (IA vs IFI prophylaxis [IFIp]), across formulations (IV, PFS and tablet) and across target population (IA paediatric vs adult).

It was noted that, as part of a previous procedure (EMEA/H/C/000610/X/0063/G), following the PK results obtained from Study 097 (IV and PFS), IV and PFS dosing schedule were selected using a target of a geomean 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 the PDCO. For the IV formulation licensing for the adult population, an upper limit of Cavg of 3650 ng/mL was set. The same targets were used (500 or 700 and 2500 ng/mL) as part of this application, but without considering the 90% proportion and without considering an upper limit.

IA vs IFI

Within each age cohort and between formulations for both IA and IFIp, Cavg are generally similar and largely above the 500 ng/mL or the 1200 ng/mL threshold. Generally, Cavg in IA vs IFIp is slightly increased in children, which is explained by the decrease of CL by 22% in IA vs IFIp (therefore increase of Cavg by the same level).

IA (IV) Paediatric vs Adult

Over 40 kg, the predicted Cavg are generally similar between children and adult, all were largely above 500 or 1200 ng/Ml.

IA (tablet) Paediatric vs Adult

A similar observation to IA (IV) can be made, except that predicted Cavg in children were generally decreased by 20% in children compared to adults. For overweight children (≥ 110 kg), approximately a 50% decrease of Cavg is predicted in children vs adults.

IA (PFS) Paediatric

No comparison PK data are available for adults. Nevertheless, the predicted Cavg in children weighing 10 to 40 kg receiving PFS are similar (but slightly decreased) to those receiving the IV formulation (same weight range).

Target attainment

For IA, within each age cohorts and between formulations, more than 96% of the virtual subjects has a Cavg ≥ 500 ng/mL and approximately 60% have a 500 ≤Cavg ≤ 2500 ng/mL.

When data are considered by weight categories, for the IV formulation and for a BW ranging from 21 to 110 kg, more than 25% (max 59.7%) of the virtual subjects are predicted to have a Cavg above 2500 ng/mL. The same hold for the PFS formulation for BW ranging from 17 to 40 kg and the tablet formulation for subject weighing 40 to <50 kg (39.8%).

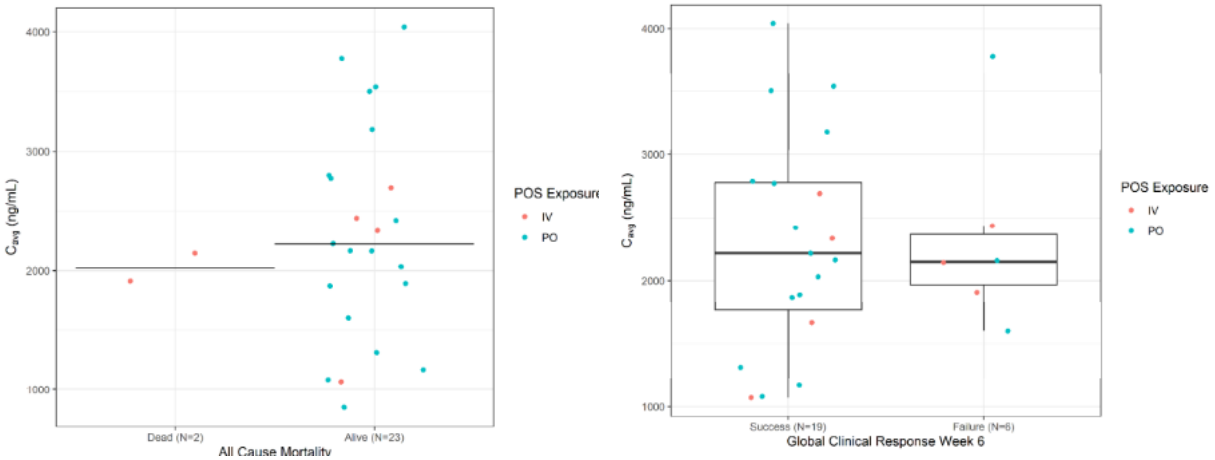
- Exposure-response analysis

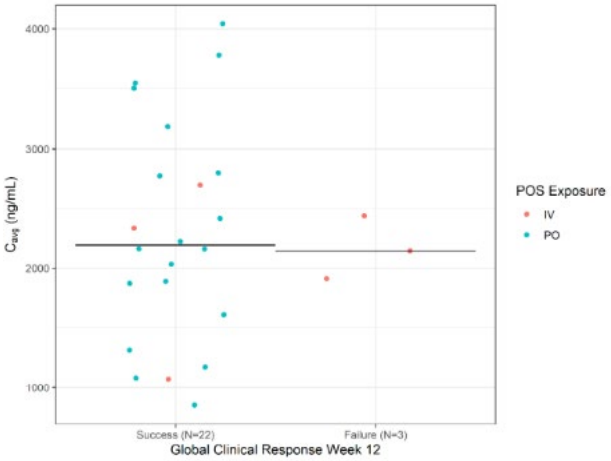
Only PK/PD data from study P104 were used for the ER analysis. Predicted Cavg from the final PPK model were used as inputs.

- ER-efficacy

The preselected efficacy endpoints included all-cause mortality, global clinical response at week 6 and Week 12. Relationship between individual predicted Cavg and these efficacy endpoints were explored graphically, as presented in Figure 9.

Figure 9: Relationship between Predicted Cavg vs Efficacy endpoints



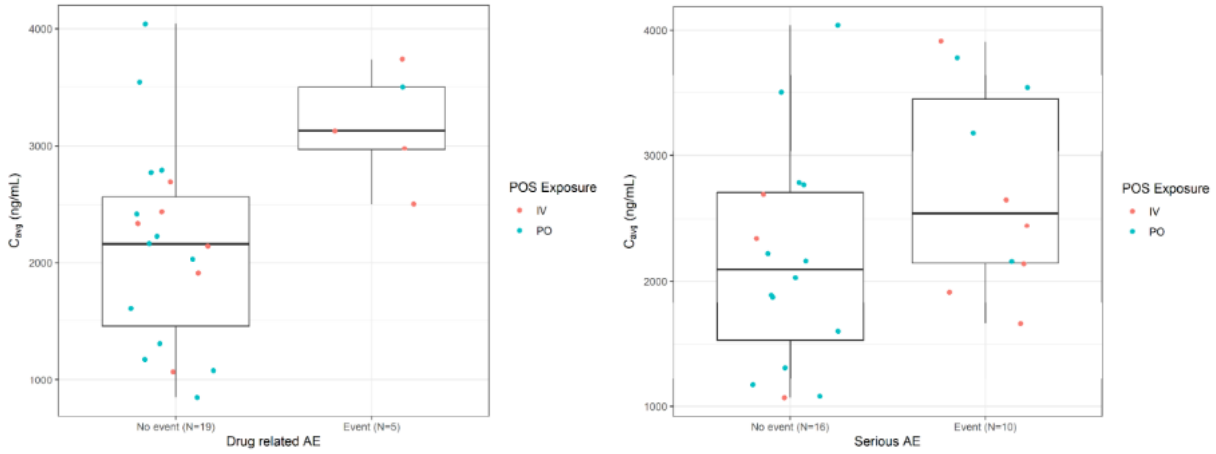


No trend was observed between Cavg and any of the efficacy endpoints.

- ER-safety

The preselected safety endpoints included drug-related adverse events (AEs) and serious AEs, including abdominal pain, ALT elevation, anaemia, arthralgia, AST elevation, constipation, decrease appetite, diarrhoea, epistaxis, fatigue, febrile neutropenia, haematuria, headache, hypertension, hypokalaemia, myalgia, nausea, pain in extremity, pyrexia, sepsis, stomatitis and vomiting. The relationship between individual predicted Cavg and AEs and serious AEs were explored graphically, as presented in Figure 10.

Figure 10: Relationship between Predicted Cavg vs Safety endpoints



No clear evidence of an increased risk of any drug-related AEs, serious AEs (drug-related or not), or any drug-related AEs that were present in at least three P104 participants, with increased POS exposure (Cavg). Although, the limited number of participants with any drug-related AE (N=4) appear to have higher POS exposures, the Cavg values are overlapping with participants with no event and across formulations. Since the exploratory analysis did not reveal any apparent trends, a model-based analysis was not conducted.

The CHMP noted that no trend in the ER efficacy analysis was observed, both responder and non – responder have an overlap of their Cavg. For the ER safety, a trend of a Cavg over 2500 ng/mL seems to be associated to drug related AE or serious AE, however as suggested by the MAH there is

an overlap of the distribution of the Cavg. Furthermore, both drug-related AE and serious AE encompass several possible safety events (as listed above).

2.3.7. Discussion on clinical pharmacology

With this application, the MAH applied to extend the use of POS IV, POS tablet and POS PFS to treatment of invasive aspergillosis (IA) in children aged ≥2 years, using a PK extrapolation approach. Therefore, in support of this application, results from the clinical Phase 2 study P104 were provided, in addition to a developed Population PK analysis (PPK) and exposure-response analysis (ER).

The PPK analysis used PK data from study P097, P104 and P127.

Study P097 was a 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, for which the PK results have been previously presented.

Study P127 was ongoing at the time of this assessment. In this study, POS PK is investigated following IV and PFS administration in children aged below 2 years for the treatment of IFIs. Therefore, the combine PK dataset cover a larger age and BW range in children aged 8 months to 17 years and weighing 5 to 102 kg, respectively.

Generally, for an extension of indication using a PK extrapolation approach, PK data observed in adults for the indication (IA, study P069) are combined with those observed in the paediatric population (IA, study P104) and a PPK analysis is performed, from which the predicted PK exposure parameters of interest in the paediatric population are compared to those from the adult reference population. However, this approach is not appropriate when for example an imbalanced number of PK samples between children and adults is observed. Therefore, the proposed approach to describe POS PK in the paediatric population only, associated to a simulation exercise (matching exposure with the adult reference target in IA) was supported.

When combining PK dataset from previous (P097), completed (P104) and ongoing (P127) studies, the method used to quantify POS should be generally the same. However, for study P097, even if the same calibration range was used (5 to 5000 ng/mL), the bioanalytical method was different to the one used for study P104, whilst for study P127 this was unknown. Since no cross-validation was performed between the two methods, the CHMP considered that there was no guarantee that the difference between the PK data from the two studies (P097 and P104) was related to a true treatment effect on CL, since both treatment and bioanalytical effects (if any) were confounded. The issue was, however, not followed up as it was considered to have no impact on the B/R.

Overall, the PPK model was fit for purpose and considered adequate to use for a simulation exercise. However, one of the assumptions made by the MAH needed further clarification: since IV, PFS and tablet formulation were used, assumption on the bioavailability (F) of the oral formulations were made. For tablets, F was fixed to 0.819 (previous application) and for PFS F was estimated at 0.849, suggesting that both formulations have the same F. However, this was not the conclusion of study P106 where the rBA of the PFS formulation was compared to the tablet formulation using a cross-over design in healthy volunteers. In this study, based on the AUC72h, it had been shown that POS PFS has a 19% increased bioavailability compared to the tablet formulation (ratio GMR [90% CI]: 1.19 [1.10-1.28]). Additional analyses were therefore performed by the MAH, which showed that

estimating F for the tablet (instead of fixed to 0.819) or inflating F of the tablet by 19% have no effect on the other PK parameter estimates, thus resolving the issue.

The simulation exercise confirmed that for all the three formulations (IV, PFS and Tablet) at the recommended dose, there is an overlap between the predicted POS Cavg in the paediatric population treated for an IA with the target Cavg in the adult reference population (IA).

With regards to target attainment, for IA, within each age cohorts and between formulations, more than 96% of the virtual subjects has a Cavg ≥ 500 ng/mL and approximately 60% have a 500 ≤Cavg ≤ 2500 ng/mL. By considering the weight categories, for the IV formulation and for a BW ranging from 21 to 110 kg, more than 25% (max 59.7%) of the virtual subjects are predicted to have a Cavg above 2500 ng/mL. The same hold for the PFS formulation for BW ranging from 17 to 40 kg and the tablet formulation for subject weighing 40 to <50 kg (39.8%). And as part of a previous application, an upper limit of 3650 ng/mL was set. The MAH was asked to provide the proportion of patient achieving a Cavg over 3650 ng/mL. In children weighing less than 40 kg, less than 10% reach this concentration with both the IV and PFS formulations. For heavier children (except ≥ 90 kg) with the IV formulation, the proportion is not negligible (10 to 19%). Nevertheless, the concern was considered to have been addressed, as it was agreed with the MAH that, to date, there were no clinical safety signals associated with a specific threshold of POS exposure.

The ER-efficacy analysis does not show a particular trend based on Cavg. For the ER-safety, a trend of a Cavg over 2500 ng/mL seems to be associated to drug related AE or serious AE. As suggested by the MAH, the CHMP agreed that there is an overlap of the distribution of the Cavg.

2.3.8. Conclusions on clinical pharmacology

Overall, the PK data of study P104, supports the use of POS IV, PFS and tablets in paediatric patients aged 2-<18 years for the treatment of IA.

2.4. Clinical efficacy

2.4.1. Main study

Title of Study

P104MK5592 A Phase 2, Open-Label, Non-Comparative Clinical Trial to Study the Safety and Efficacy of Posaconazole (POS, MK-5592) in Paediatric Participants Aged 2 to Less Than 18 Years With Invasive Aspergillosis (IA).

Methods

Study participants

- Inclusion criteria

• Male or female, and ≥2 years of age and <18 years of age at the time of first dose of study treatment and weighed at least 10 kg. Participants may be of any race/ethnicity.

• Diagnosis of possible, probable, or proven IA per EORTC/MSG disease definitions

• Central line (e.g., central venous catheter, peripherally inserted central catheter) in place or planned to be in place before beginning IV study treatment.

• Clinical symptoms consistent with an acute episode of IA, defined as duration of clinical syndrome of <30 days.

- *Exclusion criteria*

• Chronic (≥30 days' duration) IA, relapsed/recurrent IA, or refractory IA that had not responded to prior antifungal treatment.

• Cystic fibrosis, pulmonary sarcoidosis, aspergilloma, or allergic bronchopulmonary aspergillosis.

• Known hypersensitivity or other serious adverse reaction to any azole antifungal therapy, or to any other ingredient of the study treatment used.

• Any known history of torsade de pointes, unstable cardiac arrhythmia or proarrhythmic conditions, a history of recent myocardial infarction, congenital or acquired QT prolongation, or cardiomyopathy in the context of cardiac failure within 90 days of time of first dose of study treatment.

• Received any treatment specifically listed in Table 2 of the study protocol [16.1.1] within the specified timeframes before the start of study treatment.

• QTc prolongation (based on either Fridericia or Bazett's correction) at screening >500msec.

• Significant liver dysfunction (defined as total bilirubin >1.5 × ULN AND AST or ALT >3 × ULN with normal ALP) at screening.

Treatments

The study intervention administered to participants is shown below:

Table 19: Study Intervention(s)

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period	Use
Posaconazole	IV	18 mg/mL	6 mg/kg Doses are not to exceed 300 mg per administration	IV Infusion	Day 1: BID Day 2 through end of IV dosing: QD	Test Product
Posaconazole	PFS	30 mg/mL	Dosing based on weight band. To be administered to participants ≤40 kg	Oral	Days 8 – 84: QD	Test Product
Posaconazole	Tablet	100 mg	300 mg To be administered to participants >40 kg	Oral	Days 8 – 84: QD	Test Product

BID = twice daily; IV = intravenous; PFS = powder for suspension; QD = once daily.

Objectives and Outcomes/endpoints

The percentage of participants with drug-related AEs was the primary endpoint in P104, whilst efficacy outcomes were secondary endpoints. The study did not have a control arm and therefore was not designed for formal hypothesis testing of efficacy. The evaluation of efficacy of POS included assessments for global clinical response through Week 6 and 12, and for relapse of IA through 28 days post-treatment. Palatability and acceptability of the POS PFS formulation were also assessed as a secondary objective on the first and last days of the PFS intervention phase.

The objectives and endpoints are presented in the table below:

Table 20: Objectives and endpoints

Primary Objective	**Primary Endpoint**
Objective: To evaluate the safety of POS (IV and oral formulations overall)	Treatment-related AEs
Secondary Objectives	**Secondary Endpoints**
Objective: To evaluate the efficacy of POS (IV and oral formulations overall) in participants with possible, probable, or proven IA	Global clinical response (partial or complete response)
Objective: To evaluate relapse in participants with possible, probable, or proven IA who have completed treatment with POS (IV and oral formulations overall) and achieved favorable global clinical response (complete or partial)	Relapse of IA, defined as the re-emergence of clinical, radiographic, or other relevant abnormalities indicating IA
Objective: To characterize the PK of POS overall and by formulation	• Key PK parameters, consisting of C_{avg}, C_{min}, C_{max}, AUC, and T_{max}, using sparse plasma concentration sampling (steady-state trough and peak) • Analysis of exposure-response (efficacy and safety) relationships
Objective: To summarize the palatability and acceptability of POS powder for suspension (PFS) formulation	Participants' categorical perception of the taste of the PFS formulation
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Objective: To evaluate all-cause mortality in participants treated with POS (IV and oral formulations overall)	Deaths

Table 21: Global Clinical Response using 2008 EORTC/MSG Definitions

Outcome, Response	Definition
Success	
Complete response	Survival within the prespecified period of observation, resolution of all attributable symptoms and signs of disease, resolution of radiological lesion(s), and documented clearance of infected sites that are accessible to repeated sampling.
Partial response	Survival within the prespecified period of observation, improvement in attributable symptoms and signs of disease, improvement of radiological lesion(s)[a], and evidence of clearance of infected sites that are accessible to repeated sampling. In the case of radiological stabilization[b], resolution of all attributable symptoms and signs of fungal disease; or where biopsy of an infected site shows no evidence of hyphae; or where culture is negative.
Failure	
Stable response	Survival within the prespecified period of observation and minor or no improvement in fungal disease; or persistent isolation of *Aspergillus spp* or histological present in infected sites.
Progression of fungal disease	Worsening of clinical symptoms and signs of disease plus new sites of disease or radiological worsening; or persistent isolation of *Aspergillus spp* from infected sites.
Death	Death during the prespecified period of evaluation, regardless of attribution.
EORTC/MS=European Organisation for Research and Treatment of Cancer/Mycoses Study Group [a] Improvement of radiological lesions is defined as at least 25% reduction in diameter of radiological lesion. [b] Radiological stabilization is defined as 0%-25% reduction in the diameter of the lesion.	

Sample size

The planned enrolment total for this study was 30 participants. As of the Last Patient Last Visit for this report:

• Thirty-one participants were enrolled (14 in Age Cohort 1; 17 in Age Cohort 2) and included in the APaT (safety) and FAS (efficacy) analysis populations.

- Twenty-five participants were included in the responder population to evaluate relapse of IA.

• Twenty-eight participants (13 in Age Cohort 1; 15 in Age Cohort 2) were included in the primary PK population.

Randomisation and Blinding (masking)

This was open-label, non-comparative study.

Statistical methods

Key elements of the statistical analysis plan are summarized below

Table 22: Statistical and analysis methods

Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The key efficacy endpoint – overall proportion of participants in the FAS population with a favorable global clinical response at the Week 6, the Week 12, and the EOT Visits – will be estimated and the corresponding 95% confidence interval (CI) provided using the Clopper-Pearson method. In addition, the overall proportion of participants in the Responder Population who had a relapse of IA through 28 days post-treatment will be provided along with other descriptive statistics. A population PK analysis will be conducted as described in a separate Modeling Analysis Plan based on population PK models developed from prior pediatric and adult PK data for each formulation. Model-predicted individual concentration-time profiles will be used to derive C_{max}, C_{min}, C_{avg}, AUC, and T_{max}. PK parameters for POS (C_{max}, C_{min}, C_{avg}, AUC, T_{max}) derived from the population PK analysis will be listed and summarized by formulation using descriptive statistics.
Statistical Methods for Key Safety Analyses	The APaT population will be used for safety analyses. The percentage of participants who experience drug-related AEs during the treatment period plus the first 14 days of follow-up will be provided along with the corresponding 95% CI using the Clopper-Pearson method.
Interim Analyses	There is no prespecified interim analysis planned for this open-label trial. However, interim reviews of safety and efficacy data will be conducted by the external DMC in accordance with its charter.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	The sample size was chosen based on clinical, not statistical, considerations.

APaT: all participants as treated

Results

Participant flow

A total of 16 clinical investigator study sites in 9 countries enrolled participants.

A total of 34 participants were screened, and 31 participants were enrolled and received ≥1 dose of study intervention.

Most participants in Age Cohort 1 discontinued study intervention prior to Week 12 due to physician's decision. About half the participants (47.1%) in Age Cohort 2 discontinued study intervention prior to Week 12; the most common reasons were physician's decision and death. The high rates of discontinuation from study intervention due to physician decision were expected

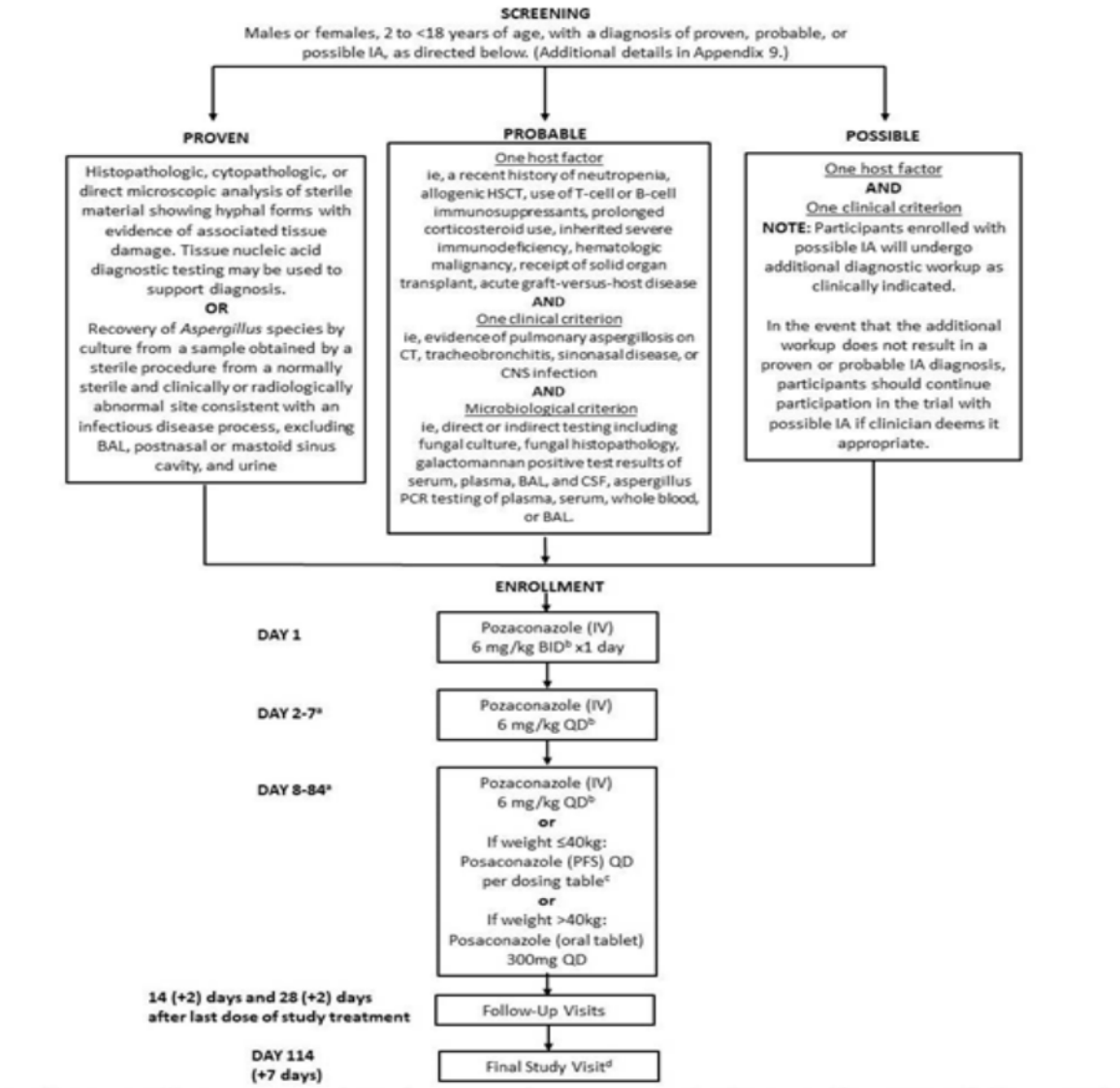
because even though participants could receive study intervention for up to 12 weeks, the actual treatment duration for each participant was based on the investigator's clinical judgment.

In both age cohorts, most participants completed the study, and the only reason for discontinuation from the study was death.

Three participants who were screened but not enrolled: they were screen failures who did not meet inclusion criteria or met exclusion criteria.

No participants from either age cohort discontinued from study intervention or the study due to COVID-19.

Figure 11: Study Design



a. All participants will initiate treatment with IV study treatment and may transition to oral study treatment after a minimum of 7 days on IV study treatment and as clinically indicated, as described in Section 4.3. The planned duration of study treatment is 6 to 12 weeks (42 to 84 days); the actual treatment duration for each participant will be based on clinical judgment of the investigator.
b. To a maximum dose of 300mg per administration.
c. Refer to Table 1 in Section 4.3.1 for weight-based dosing of the formulation for participants weighing ≤40kg.
d. Mortality will be assessed through the Day 114 visit for all participants

Recruitment

First Participant enrolled: 02-JUL-2020

Last participant last visit: 18-DEC-2023

Conduct of the study

This study was conducted in accordance with local and/or national regulations (including all applicable data protection laws and regulations), ICH GCP and with the ethical principles that have their origin in the Declaration of Helsinki regarding IEC review, informed consent, and the protection of human participants in biomedical research (MSD Code of Conduct for Interventional Clinical Trials.

Part of this study was conducted during the COVID-19 pandemic. The Sponsor continued to follow its SOPs for study conduct, monitoring, and oversight during the pandemic and employed a risk-based approach to assess and mitigate impact on study conduct.

Changes in the conduct of the study implemented by protocol amendment are summarized in the table below. There were no changes in the planned conduct of the study implemented by protocol amendment due to the COVID-19 pandemic.

Table 23: Protocol Amendments for MK-5592-104

Document	Date of Issue	Overall Rationale
Amendment 04	02-SEP-2022	To revise exclusion criteria to include the specific K values used in the modified Schwartz formula for males of different ages.
Amendment 03	19-JUL-2022	To 1) align dosing of the powder for suspension formulation with the dosing algorithm given in the approved product labeling for paediatric use, 2) update the definitions of possible, probable, or proven IA to align with the 2020 EORTC/MSG criteria, and 3) update the prohibited and allowed medications lists to align with approved product labeling.
Amendment 02	15-DEC-2020	To provide details for IV dosing requirements; to clarify procedures (i.e., ECG and diagnostic imaging) in the Schedule of Activities; to clarify maximum blood volume and method for calculating creatinine clearance; to remove pregnancy exclusion to avoid potential confusion with the pregnancy criteria in the list of inclusions; and to update informed consent text to align with current informed consent/assent procedures.

Amendment 01	21-APR-2020	To remove the device-related adverse event reporting language and the Future Biomedical Research (FBR) substudy from the protocol.
Original Protocol	17-JUL-2019	Not applicable

ECG = electrocardiograms; EORTC/MSG = European Organisation for Research and Treatment of Cancer/Mycoses Study Group; IA = invasive aspergillosis; IV = intravenous.

Important protocol deviations were reported for 9 (29.0%) participants. Of these, 8 (25.8%) participants had important protocol deviations that were considered to be clinically important. The most frequently reported clinically important protocol deviation (12.9%) was related to study procedures wherein at specific timepoints either global clinical response was not assessed, or PK samples were not collected.

No participant's data were excluded from analysis due to a protocol deviation.

No protocol deviations were classified as a serious GCP compliance issue.

Baseline data

Table 24: Participant Characteristics All Enrolled Participants

	Age Cohort 1 (2 -< 12 years old)		Age Cohort 2 (12 -< 18 years old)		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	14		17		31	
Sex						
Male	7	(50.0)	16	(94.1)	23	(74.2)
Female	7	(50.0)	1	(5.9)	8	(25.8)
Age (Years)						
2 -< 12	14	(100.0)	0	(0.0)	14	(45.2)

12 -< 18	0	(0.0)	17	(100.0)	17	(54.8)
Mean	6.9		14.5		11.1	
SD	2.7		1.7		4.4	
Median	8.0		14.0		12.0	
Range	2 to11		12 to 17		2 to 17	
Race						
Asian	3	(21.4)	5	(29.4)	8	(25.8)
Multiple	2	(14.3)	4	(23.5)	6	(19.4)
American Indian Or Alaska Native, White	2	(14.3)	4	(23.5)	6	(19.4)
White	9	(64.3)	8	(47.1)	17	(54.8)
Ethnicity						

Hispanic Or Latino	2	(14.3)	5	(29.4)	7	(22.6)
Not Hispanic Or Latino	12	(85.7)	12	(70.6)	24	(77.4)

Demographic and baseline characteristics were generally comparable between the age cohorts, except for sex. Age Cohort 1 had an equal number of male and female participants while almost all participants in Age Cohort 2 were male.

Overall, approximately half of the participants were white, and the majority of participants were not Hispanic or Latino. The median age for Age Cohort 1 was 8.0 years old (2 to 11 years) and for Age Cohort 2 was 14.0 years old (12 to 17 years).

Overall, 71.0% of participants had possible IA, 22.6% of participants had probable IA, and 6.5% of participants had proven IA. More participants in Age Cohort 1 had possible or proven IA than in Age Cohort 2.

Numbers analysed

• Thirty-one participants were enrolled (14 in Age Cohort 1; 17 in Age Cohort 2) and included in the APaT (safety) and FAS (efficacy) analysis populations.

- Twenty-five participants were included in the responder population to evaluate relapse of IA.

• Twenty-eight participants (13 in Age Cohort 1; 15 in Age Cohort 2) were included in the primary PK population.

Outcomes and estimation

Efficacy results

- Extent of Exposure

Participants received study intervention for an overall median duration (range) of 49 days (2 to 88 days).

Exposures for participants who received IV intervention and/or transitioned to oral interventions are described below:

- The median duration (range) of IV intervention was 8 days (2 to 78 days).
- Nine participants received only POS IV and did not transition to oral intervention.
- Twelve participants were transitioned to POS tablets and the median duration (range) was 67.5 days (6 to 80 days).

- Ten participants were transitioned to POS PFS and the median duration (range) was 48 days (7 to 76 days).
- Twenty-one participants received at least 7 days of POS IV therapy and transitioned to oral therapy (either PFS or tablet) for at least 7 days.
- Secondary efficacy endpoint: Global Clinical Response Through Week 6 and Week 12 (Full Analysis Set Population) is presented in the tables below.

Table 25: Analysis of Global Clinical Response Through Week 6 and Week 12

Full Analysis Set Population

Outcome	Age Cohort 1 (2 -< 12 years old) n/N (%)	Age Cohort 2 (12 -< 18 years old) n/N (%)	Total n/N (%)	95% CI[a]
Week 6				
Success	9/14 (64.3)	12/17 (70.6)	21/31 (67.7)	(48.6, 83.3)
Failure	4/14 (28.6)	5/17 (29.4)	9/31 (29.0)	
Missing	1/14 (7.1)	0/17 (0.0)	1/31 (3.2)	
Week 12				
Success	11/14 (78.6)	13/17 (76.5)	24/31 (77.4)	(58.9, 90.4)
Failure	3/14 (21.4)	4/17 (23.5)	7/31 (22.6)	

[a] Based on the Clopper-Pearson method for the 2-sided exact 95% confidence interval (CI) on a binomial proportion [Clopper, C. J. and Pearson, E. S. 1934].
The investigator assessed global clinical response using the 2008 European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) disease definition at the Week 6 and Week 12 visits; in the event of early therapy discontinuation, global clinical response was assessed at the EOT Visit (prior to Weeks 6 or 12 visit).
The Week 6 assessment included a visit window of +/- 2 weeks; participants who stopped study therapy prior to the Week 6 Visit and had an end of treatment (EOT) visit were included in the Week 6 outcome (ie, if no Week 6 Visit, assessment at EOT Visit prior to Week 6 Visit was carried forward).
Any death prior to Week 6 was considered as a Failure at Week 6.
The Week 12 assessment included a visit window of +/- 4 weeks; participants who stopped study therapy prior to the Week 12 Visit and only had a Week 6 Visit or an end of treatment (EOT) Visit after the Week 6 Visit were included in the Week 12 outcome (ie, if no Week 12 visit, assessment at Week 6 Visit or EOT Visit after the Week 6 Visit was carried forward).
Any death prior to Week 12 was considered as a Failure at Week 12.

Table 26: Summary of Global Clinical Response Through Week 6 and Week 12 Full Analysis Set Population

Global Clinical Response	Age Cohort 1 (2 -< 12 years old) n/N (%)	Age Cohort 2 (12 -< 18 years old) n/N (%)	Total n/N (%)
Through Week 6			
Success, Complete Response	6/14 (42.9)	3/17 (17.6)	9/31 (29.0)
Success, Partial Response	3/14 (21.4)	9/17 (52.9)	12/31 (38.7)
Failure, Stable Response	2/14 (14.3)	2/17 (11.8)	4/31 (12.9)
Failure, Progression of Fungal Disease	1/14 (7.1)	0/17 (0.0)	1/31 (3.2)
Failure, Death During the Period of Evaluation	1/14 (7.1)	3/17 (17.6)	4/31 (12.9)
Missing	1/14 (7.1)	0/17 (0.0)	1/31 (3.2)
Through Week 12			
Success, Complete Response	8/14 (57.1)	7/17 (41.2)	15/31 (48.4)
Success, Partial Response	3/14 (21.4)	6/17 (35.3)	9/31 (29.0)
Failure, Stable Response	1/14 (7.1)	1/17 (5.9)	2/31 (6.5)
Failure, Progression of Fungal Disease	1/14 (7.1)	0/17 (0.0)	1/31 (3.2)
Failure, Death During the Period of Evaluation	1/14 (7.1)	3/17 (17.6)	4/31 (12.9)

Among participants with possible IA (n=22):

- The percentage of participants with a favourable global clinical response through both time periods (Week 6 and Week 12) was 68.2% (n=15),
- The percentage of participants with an unfavourable global clinical response through both time periods was 22.7% (n=5),

- The percentage of participants with an unfavourable global clinical response through Week 6 but a favourable global clinical response through Week 12 was 4.5% (n=1), and
- The percentage of participants with missing data through Week 6 and a favourable global clinical response through Week 12 was 4.5% (n=1).

Among participants with probable IA (n=7):

- The percentage of participants with a favourable global clinical response through both time periods was 71.4% (n=5), and
- The percentage of participants with an unfavourable global clinical response through both time periods was 28.6% (n=2).

Among participants with proven IA (n=2):

- One participant (50%) had an unfavourable global clinical response through Week 6 but a favourable global clinical response through Week 12, and
- The other participant (50%) had a favourable global clinical response through both time periods.

- Relapse of IA

No participant in the responder population had a relapse of IA through 28 days post-treatment. One participant died at 11 days post-treatment due to "worsening of acute lymphoblastic leukaemia with hepatic extra-medullary involvement," so relapse of IA through 28 days post-treatment was not assessed.

Table 27: Summary of Relapse of IA Through 28 Days Post-treatment Responder Population

Outcome	Age Cohort 1 (2 -< 12 years old) n/N (%)	Age Cohort 2 (12 -< 18 years old) n/N (%)	Total n/N (%)
Relapse of IA	0/12 (0.0)	0/13 (0.0)	0/25 (0.0)
No Relapse of IA	11/12 (91.7)	13/13 (100.0)	24/25 (96.0)
Not Assessed	1/12 (8.3)	0/13 (0.0)	1/25 (4.0)

Relapse of Invasive Aspergillosis (IA) infection - defined as the re-emergence of clinical, radiographic, or other relevant abnormalities indicating IA was assessed by the investigator through 28 days following completion of study treatment only in participants who achieved favourable global clinical response (e.g., partial or complete response).

One participant had an early in-person follow-up visit on Day 26 post-treatment and the relapse assessment was then conducted via telephone contact on Day 28 post-treatment. One participant was "Not Assessed" for relapse of IA through 28 days following completion of study treatment because of death due to "worsening of acute lymphoblastic leukemia with hepatic extramedullary involvement" 11 days post-treatment.

- Palatability and Acceptability Results

Assessment of palatability and acceptability of the POS PFS formulation on the first and last days of the PFS treatment phase was reported for 10 participants. Most participants (90%) reported PFS as tasting "very good," "good," or "neither good nor bad" on the first and last days of PFS. None of the participants reported any problems taking the PFS dose.

Table 28: Summary of Palatability and Acceptance Categorical Perception for PFS All Participants as Treated with PFS

	First Day on PFS n (%)	Last Day on PFS n (%)
Number of Participants Completing Palatability Questionnaire	10	10
Person Completing the Palatability Questionnaire		
The health care provider (e.g., physician, nurse, medical assistant or nursing assistant caring for the patient)	2 (20.0)	2 (20.0)
The parent/primary caregiver	4 (40.0)	4 (40.0)
The patient	3 (30.0)	3 (30.0)
The patient and parent/primary caregiver	1 (10.0)	1 (10.0)
Taste		
Very good	2 (20.0)	1 (10.0)

Good	4 (40.0)	4 (40.0)
Very bad	1 (10.0)	1 (10.0)
Neither good nor bad	3 (30.0)	4 (40.0)
Problems Taking Dose		
Any problem	0 (0.0)	0 (0.0)
Refusing	0 (0.0)	0 (0.0)
Spitting out	0 (0.0)	0 (0.0)
Vomiting or spitting up	0 (0.0)	0 (0.0)
Gagging	0 (0.0)	0 (0.0)

- All-cause Mortality

The incidence of all-cause mortality in the APaT (All participants as Treated) population was 4/31 (12.9%) through Day 42 and remained the same through the end of the study (Day 114). More participants died in Age Cohort 2 (3/17, 17.6%) than Age Cohort 1 (1/14, 7.1%).

Table 29: Summary of All-cause Mortality Through Day 42 and Day 114 All Participants as Treated

	Age Cohort 1 (2 -< 12 years old)	Age Cohort 2 (12 -< 18 years old)	Total
	n (%)	n (%)	n (%)
Participants in population	14	17	31
Day 42 Status for Trial			

Alive	13	(92.9)	14	(82.4)	27	(87.1)
Dead	1	(7.1)	3	(17.6)	4	(12.9)
Day 114 Status for Trial						
Alive	13	(92.9)	14	(82.4)	27	(87.1)
Dead	1	(7.1)	3	(17.6)	4	(12.9)

The CHMP noted that, globally, the efficacy results observed in the P104 study suggest good clinical outcomes in this critical disease. These results are in accordance with data observed in adults with the same disease.

However, the data are only descriptive, since this study was not designed to demonstrate efficacy, but with priority to cumulate the safety and PK data in children with IA.

2.4.2. Discussion on clinical efficacy

In P104, an open-label, non-comparative study, efficacy outcomes were secondary endpoints, and the study was not powered for formal hypothesis testing.

The global clinical response analyses through Weeks 6 and 12 were performed on the FAS population consisting of all 31 enrolled participants who had possible, probable, or proven IA (based on modified 2020 EORTC/MSG definitions) as classified by the investigator, had one or more post-allocation observation for the analysis endpoint after one or more dose of study intervention, and had baseline data for those analyses that require baseline data.

Thirty-one (31) patients were included. The median age for Age Cohort 1 (n=14) was 8.0 years old (2 to 11 years) and for Age Cohort 2 (n=17) was 14.0 years old (12 to 17 years). Chronic (≥30 days' duration) IA, relapsed/recurrent IA, or refractory IA that had not responded to prior antifungal treatment were excluded of the study.

The majority (67.7%, 95% CI: 48.6, 83.3) of participants in the FAS population achieved a favourable global clinical response (success) through Week 6. A greater percentage of participants achieved a favourable global clinical response through Week 12 (77.4%, 95% CI: 58.9, 90.4) compared with Week 6. The percentage of participants who achieved complete response increased from 29.0% through Week 6 to 48.4% through Week 12.

No participant in the responder population had a relapse of IA through 28 days post-treatment.

It should be emphasised that the majority of patients had possible IA (22/31) at baseline (i.e. without microbiological confirmation of IA), which is one of the limitations of the study.

Assessment of palatability and acceptability of the POS PFS formulation on the first and last days of the PFS treatment phase was reported for 10 participants. Most participants (90%) reported PFS as

tasting "very good", "good", or "neither good nor bad" on the first and last days of PFS. None of the participants reported any problems taking the PFS dose.

The incidence of all-cause mortality in the APaT population was 12.9% through Day 42 and remained the same through the end of the study (Day 114). More participants died in Age Cohort 2 than Age Cohort 1.

2.4.3. Conclusions on the clinical efficacy

The CHMP considered that the descriptive efficacy data observed in a paediatric population from 2 years old with possible, probable or proven Invasive Aspergillosis, albeit with some limitations (open-label, non-comparative study with safety as primary endpoint and a limited sample size), indicate favourable outcomes.

It was noted that most included patients had 'possible IA' (22/31) at baseline (i.e. without microbiological confirmation of IA), another limitation of the study. Chronic (≥30 days' duration) IA, relapsed/recurrent IA, or refractory IA that had not responded to prior antifungal treatment were excluded of the study corresponding to the scope of this variation (extension of indication for children in first-line therapy of IA).

However, these efficacy results can only be considered supportive of the PK data that allowed extrapolation of the clinical data available in adults with IA to the paediatric population.

2.5. Clinical safety

Introduction

The evaluation of safety of POS (IV, PFS, and tablet formulations) was the primary objective of P104 and the percentage of participants with drug-related AEs was the primary endpoint. Safety analyses were based on the APaT population, which included 31 enrolled participants who received ≥1 dose of study intervention, regardless of their IA classification (possible, probable, or proven IA). AEs were reported from the time of intervention allocation through 14 days following cessation of study intervention. A survival assessment was also performed through the end of the study visit (Day 114).

Patient exposure

A total of 31 participants were enrolled and received ≥1 dose of study intervention.

Most participants (92.9%, 13/14) in Age Cohort 1 discontinued study intervention prior to Week 12, and the most common reason for discontinuation was due to physician decision. About half the participants (47.1%, 8/17) in Age Cohort 2 discontinued study intervention prior to Week 12, and the most common reasons were physician decision and death. The rate of discontinuation from study intervention due to physician decision was expected because although participants could receive study intervention for up to 12 weeks, the actual treatment duration for each participant was based on the investigator's clinical judgment.

If the investigator considered intervention of less than 12 weeks to be sufficient and the participant's global clinical response was favourable, the participant's study intervention disposition was considered to be discontinued due to physician decision.

In both age cohorts, most participants (87.1%, 27/31) completed the study, and the only reason for discontinuation from the study was death (12.9%, 4/31), which is not unexpected in this study population of paediatric participants with IA.

Demographic and baseline characteristics were generally comparable between the age cohorts, except for sex. Age Cohort 1 had an equal number of male and female participants while almost all participants (94.1%, 16/17) in Age Cohort 2 were male. Overall, 71.0% (22/31) of participants had possible IA, 22.6% (7/31) of participants had probable IA, and 6.5% (2/31) of participants had proven IA.

Overall, approximately half of the participants (54.8%) were white, and the majority of participants (77.4%) were not Hispanic or Latino. The median age for Age Cohort 1 was 8.0 years and for Age Cohort 2 was 14.0 years. Overall, 71.0% of participants had possible IA, 22.6% of participants had probable IA, and 6.5% of participants had proven IA. More participants in Age Cohort 2 had probable IA than in Age Cohort 1.

Disposition of Participants. All Enrolled Participants

	Age Cohort 1 (2 -< 12 years old)		Age Cohort 2 (12 -< 18 years old)		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	14		17		31	
Participant Study Medication Disposition						
Started	14		17		31	
Completed	1	→ (7.1)	9	→ (52.9)	10	→ (32.3)
Discontinued	13	→ (92.9)	8	→ (47.1)	21	→ (67.7)
Adverse Event	1	→ (7.1)	1	→ (5.9)	2	→ (6.5)
Death	0	→ (0.0)	3	→ (17.6)	3	→ (9.7)
Physician Decision	12	→ (85.7)	4	→ (23.5)	16	→ (51.6)
Participant Study Disposition						
Completed	13	→ (92.9)	14	→ (82.4)	27	→ (87.1)
Discontinued	1	→ (7.1)	3	→ (17.6)	4	→ (12.9)
Death	1	→ (7.1)	3	→ (17.6)	4	→ (12.9)

Participants received study intervention for an overall median duration (range) of 49 days (2 to 88 days).

Exposures for participants who received IV intervention and/or transitioned to oral interventions are described below:

- The median duration (range) of IV intervention was 8 days (2 to 78 days).
- Nine participants received only POS IV and did not transition to oral intervention.
- Twelve participants were transitioned to POS tablets and the median duration (range) was 67.5 days (6 to 80 days).
- Ten participants were transitioned to POS PFS and the median duration (range) was 48 days (7 to 76 days).
- Twenty-one participants received at least 7 days of POS IV therapy and transitioned to oral therapy (either PFS or tablet) for at least 7 days.

Adverse events

As anticipated for this study population of paediatric participants with IA, AEs were reported for most of the participants in the APaT population (85.7% [12/14] of participants in Age Cohort 1 and 88.2% [15/17] of participants in Age Cohort 2). Drug-related AEs were reported for 22.6% (7/31) of participants (95% CI: 9.6, 41.1).

SAEs were reported for 38.7% (12/31) of participants (4 in Age Cohort 1 and 8 in Age Cohort 2) and deaths due to AEs were reported for 12.9% (4/31) of participants (1 in Age Cohort 1 and 3 in Age Cohort 2). None of the SAEs or deaths due to AEs were considered drug-related by the investigator. One participant in each age cohort discontinued study intervention due to an AE.

Adverse Event Summary. All Participants as Treated

	Age Cohort 1 (2 -< 12 years old)		Age Cohort 2 (12 -< 18 years old)		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	14		17		31	
with one or more adverse events	12	(85.7)	15	(88.2)	27	(87.1)
with no adverse event	2	(14.3)	2	(11.8)	4	(12.9)
with drug-related adverse events	2	(14.3)	5	(29.4)	7	(22.6)
with serious adverse events	4	(28.6)	8	(47.1)	12	(38.7)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	1	(7.1)	3	(17.6)	4	(12.9)
discontinued drug due to an adverse event	1	(7.1)	1	(5.9)	2	(6.5)
discontinued drug due to a drug-related adverse event	0	(0.0)	1	(5.9)	1	(3.2)
discontinued drug due to a serious adverse event	1	(7.1)	0	(0.0)	1	(3.2)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)

→ Determined by the investigator to be related to the drug.¶
Adverse events were followed for up to and including 14 days after the last dose.

Overall, the four most frequently reported AEs were vomiting (32.3%), pyrexia (29.0%), hypertension (25.8%), and abdominal pain (19.4%).

AEs considered by the investigator to be drug-related were reported for seven participants (2 in Age Cohort 1 and five in Age Cohort 2). The only drug-related AEs reported for >1 participant in either Age Cohort were 'ALT increased' and 'AST increased', both reported for two participants in Age Cohort 2.

A drug-related AE meeting the criteria for an ECI (liver function test increased) was reported for one participant in Age Cohort 2 on Day 2. Per protocol, study intervention was discontinued; the participant was asymptomatic, and the event was considered by the investigator to be resolved by Day 3.

All drug-related AEs were Grades 1 or 2 in severity and resolved before the end of the study; no action was taken with study intervention due to these events.

Within Group Analysis of Participants With Drug-related Adverse Events. (Incidence > 0% in One or More Treatment Groups) by Age Cohorts. All Participants as Treated

	Age Cohort 1 (2 -< 12 years old)			Age Cohort 2 (12 -< 18 years old)			Total		
	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]	n	(%)	(95% CI)[a]
Participants in population	14	14		17	17		31	31	
with one or more drug-related adverse events	2	(14.3)	(1.8, 42.8)	5	(29.4)	(10.3, 56.0)	7	(22.6)	(9.6, 41.1)
with no drug-related adverse events	12	(85.7)	(57.2, 98.2)	12	(70.6)	(44.0, 89.7)	24	(77.4)	(58.9, 90.4)
Gastrointestinal disorders	**1**	**(7.1)**	**(0.2, 33.9)**	**1**	**(5.9)**	**(0.1, 28.7)**	**2**	**(6.5)**	**(0.8, 21.4)**
Abdominal pain upper	0	(0.0)	(0.0, 23.2)	1	(5.9)	(0.1, 28.7)	1	(3.2)	(0.1, 16.7)
Nausea	0	(0.0)	(0.0, 23.2)	1	(5.9)	(0.1, 28.7)	1	(3.2)	(0.1, 16.7)
Vomiting	1	(7.1)	(0.2, 33.9)	0	(0.0)	(0.0, 19.5)	1	(3.2)	(0.1, 16.7)
General disorders and administration site conditions	**0**	**(0.0)**	**(0.0, 23.2)**	**1**	**(5.9)**	**(0.1, 28.7)**	**1**	**(3.2)**	**(0.1, 16.7)**
Feeling hot	0	(0.0)	(0.0, 23.2)	1	(5.9)	(0.1, 28.7)	1	(3.2)	(0.1, 16.7)
Injury, poisoning and procedural complications	**1**	**(7.1)**	**(0.2, 33.9)**	**0**	**(0.0)**	**(0.0, 19.5)**	**1**	**(3.2)**	**(0.1, 16.7)**
Infusion related reaction	1	(7.1)	(0.2, 33.9)	0	(0.0)	(0.0, 19.5)	1	(3.2)	(0.1, 16.7)
Investigations	**0**	**(0.0)**	**(0.0, 23.2)**	**3**	**(17.6)**	**(3.8, 43.4)**	**3**	**(9.7)**	**(2.0, 25.8)**
Alanine aminotransferase increased	0	(0.0)	(0.0, 23.2)	2	(11.8)	(1.5, 36.4)	2	(6.5)	(0.8, 21.4)
Aspartate aminotransferase increased	0	(0.0)	(0.0, 23.2)	2	(11.8)	(1.5, 36.4)	2	(6.5)	(0.8, 21.4)
Liver function test increased	0	(0.0)	(0.0, 23.2)	1	(5.9)	(0.1, 28.7)	1	(3.2)	(0.1, 16.7)

[a] Based on the exact binomial method proposed by Clopper and Pearson.
Every participant 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 reported from the first dose of study treatment through 14 days after the last dose.
Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 is used in the reporting of this study.

Source: [P104MK5592: adam.adsl; adae]

Overall, AEs with maximum Grades 1 or 2 severity were reported for 5 (16.1%) and 6 (19.4%) participants, respectively. Ten (32.3%) participants had maximum Grade 3 AEs. The most frequently reported Grade 3 AE was febrile neutropenia, reported for a total of 3 participants.

Two (6.5%) participants had maximum Grade 4 AEs (1 participant with gastroenteritis clostridial, and 1 participant with pneumonia, adenovirus infection, and viral sepsis). None of the Grade 4 AEs were considered drug-related by the investigator; and all were resolved (gastroenteritis clostridial, pneumonia, and viral sepsis) or resolving (adenovirus infection) by the last study visit.

Four (12.9%) participants had maximum Grade 5 (death) AEs.

The Committee considered that, in study P104, the safety profile for POS is well-established.

In this critically ill population, the most frequently reported AEs were vomiting, pyrexia, hypertension and abdominal pain. AEs considered drug-related by the investigator were reported for 7 participants and were: vomiting (n = 1), infusion related reaction (n = 1), abdominal pain upper (n = 1), nausea (n = 1), feeling hot (n = 1), ALAT (n = 2) and ASAT (n = 2) increased.

Serious adverse event/deaths/other significant events

Deaths

Deaths due to AEs were reported for 12.9% (4/31) of participants during the study. The one death in Age Cohort 1 was due to leukemic infiltration extramedullary and the three deaths in Age Cohort 2 (1 participant each) were due to pulmonary haemorrhage, hematemesis, and thrombocytopenia. None of the deaths were considered drug-related by the investigator.

Other Serious Adverse Events

Overall, SAEs were reported for 38.7% (12/31) of participants. The two most frequently reported SAEs were febrile neutropenia and sepsis (2 participants each, 6.5%). No SAEs were considered drug-related by the investigator. One participant in Age Cohort 1 discontinued study intervention due to an SAE (leukemic infiltration extramedullary) with a fatal outcome.

No SAEs were considered drug-related by the investigator.

Other Significant Adverse Events

Two participants discontinued study intervention due to an AE: one in Age Cohort 1 with a fatal outcome (leukemic infiltration extramedullary) and one in Age Cohort 2 with an ECI (liver function test increased); the ECI of liver function test increased resolved by Day 3.

The participant in Age Cohort 2 had laboratory values that met the protocol-defined ECI criteria for a potential DILI event (liver function test increased). This participant discontinued study intervention due to the event. Additional testing did not reveal an obvious alternative cause of the elevated liver function tests. The event was considered drug-related by the investigator and resolved by Day 3, and the participant completed the study.

Laboratory findings

Most participants had Grades 1 or 2 chemistry lab abnormalities and Grades 3 or 4 neutrophil reductions at baseline and during the study.

For the majority of participants, there were no clinically meaningful findings in laboratory values (haematology and chemistry) that met predetermined limits of change criteria based on Common Terminology Criteria for Adverse Events version 5.0.

During the study, 21 (67.8%) participants had elevations in ALT or AST that met predetermined criteria, 5 (16.1%) participants had elevations in bilirubin and 4 (12.9%) participants had elevations in alkaline phosphatase.

No clinically meaningful changes were observed in mean changes in vital sign measurements (i.e., systolic/diastolic blood pressure, temperature, respiratory rate, and heart rate) from baseline over time for both age cohorts.

Overall, 2 participants (1 in each age cohort) had a QTc value ≥500 msec during the intervention phase. One participant did not have this event reported as an AE, and the other participant had ECG QT prolonged reported twice as an AE that was not considered drug-related by the investigator. The prolonged QTc values in both participants resolved. Confounding factors were noted among both participants. Both participants remained on study intervention without interruption and completed the study.

Safety in special populations

The percentage of participants with AEs was generally comparable for both age cohorts. No clinically meaningful differences between age cohorts in percentage of participants with AEs were observed for any AE category in P104. Evaluations of the safety of POS by intrinsic factors other than age (e.g., gender, race) were not performed for P104 as there were insufficient numbers of participants to perform subgroup analyses of these variables.

Safety related to drug-drug interactions and other interactions

DDIs were not specifically evaluated in study P104. No new DDI studies were conducted for the paediatric indication.

Discontinuation due to adverse events

Based on the cumulative data in the clinical development programme, no safety signal was identified that would suggest a potential for withdrawal or rebound effects after discontinuing POS.

The CHMP considered that, in P104, the evaluation of safety of POS (IV and oral formulations overall) was the primary objective of the study and drug-related AEs were the primary endpoint.

Safety analyses were performed on the APaT population, which included all 31 enrolled participants who received ≥1 dose of study intervention. The 4 most frequently reported AEs were vomiting (32.3%), pyrexia (29.0%), hypertension (25.8%), and abdominal pain (19.4%).

AEs considered drug-related by the investigator were reported for 7 participants (2 in Age Cohort 1 and 5 in Age Cohort 2). The most frequently reported drug-related AEs (6.5%) were ALT increased and AST increased, both reported for 2 participants in Age Cohort 2. A drug-related AE meeting the criteria for an ECI (liver function test increased) was reported for 1 participant in Age Cohort 2 (for a potential DILI event). This participant experienced AST and ALT increased on Day 2. The participant remained asymptomatic, but study medication was discontinued due to the event of Grade 2 LFT increased. The participant's clinical response on Day 2 was considered to be a stable response. On Day 3 local laboratory test results showed increased ALT of 185 U/L (NR: 0-41) and AST was at 13 U/L (NR: 0-40), and LFT increased was considered resolved. Subsequent laboratory testing showed full recovery of the LFTs by Day 30. In the opinion of the investigator, the non-serious AE and ECI of LFT increased was related to the study medication. At the last date of contact on Day 115, the participant was alive and had completed the study. The participant did not experience any other drug-related serious or non-serious AEs, as assessed by the investigator.

All drug-related AEs were Grades 1 or 2 in severity and resolved.

Deaths due to AEs were reported for 4 (12.9%) participants during the study. There was 1 death in Age Cohort 1 due to leukemic infiltration extramedullary and 3 deaths in Age Cohort 2 due to pulmonary haemorrhage, hematemesis, and thrombocytopenia. None of the deaths were considered drug-related by the investigator.

SAEs were reported for 12 (38.7%) participants. The 2 most frequently reported SAEs (6.5%) were febrile neutropenia and sepsis. No SAEs were considered drug-related by the investigator.

Overall, 2 participants (1 in each age cohort) had a QTc value ≥500 msec during the treatment phase. The prolonged QTc values in both participants resolved. Both participants remained on study intervention without interruption and completed the study. One participant did not have this event reported as an AE, and the other participant had "electrocardiogram QT prolonged" reported twice as an AE that was not considered drug related by the investigator. Nevertheless, the MAH was requested to provide the CIOMS of these AE. The MAH provided relevant data for these two non-serious AEs of "electrocardiogram QT prolonged." Both AEs were considered not related, and the outcome was "recovered".

Having in mind that on this small sample size:

- a drug-related AE meeting the criteria for an ECI (liver function test increased) was reported for 1 participant in Age Cohort 2 (for a potential DILI event)
- 2 participants (1 in each age cohort) had a QTc value ≥500 msec during the treatment phase.

The MAH was asked to discuss the likelihood of a trend for more severity EA in the targeted younger population, in relation with a potential trend for over-exposure. In summary, the pharmacokinetic

modelling conducted over the course of the clinical development programme has not demonstrated an exposure-response relationship related to safety, and an upper limit of exposure has never been established. Each of the specific events noted by the CHMP either occurred very soon after study medication administration (after only 1 or 2 doses of posaconazole IV), were confounded by other factors (e.g., medical history, concomitant medications), or were not associated with elevated posaconazole plasma concentrations (e.g., <2000 ng/mL). In addition, the events did not cluster in participants of younger ages, suggesting no association between safety events and age. The aggregate safety data of Study P104 similarly do not support a trend related to posaconazole use and liver function test or QTc interval abnormalities in this paediatric population. The safety data do not suggest a trend for greater severity of AEs in this younger population or an association with posaconazole over-exposure. The CHMP agreed that, from safety point of view, the data do not suggest a trend for greater severity of AEs in this younger population.

Post marketing experience

Since its first approval in the EU on 25-OCT-2005 for POS oral suspension, as of 25-OCT-2024, POS has been registered and approved for use in 76 countries. Currently, there are 4 marketed formulations of POS. Each formulation and date of first approval worldwide is listed below.

- Oral suspension, 25-OCT-2005
- Tablet, 25-NOV-2013
- IV solution, 13-MAR-2014
- PFS, 31-MAY-2021

There are no records of any registration being revoked or withdrawn for safety reasons.

A summary of the worldwide distribution of POS from market introduction (for each formulation) to 25-OCT-2024 is presented below. Patient exposure estimates for POS were calculated from information gathered and maintained by external source, from the MAH's internal distribution data and databases.

Total cumulative patient exposure for POS (from market introduction for each formulation) through 25-OCT-2024 was approximately 173,268 patient-years of treatment (64,489 for the oral suspension, 105,725 for tablets, 2995 for the IV solution, and 59 for the PFS).

The MAH's global safety database was queried for valid, spontaneous, and noninterventional study sources for each formulation, from market introduction through 25OCT-2024. Overall, 26,451 AEs have been reported in a total of 11,452 reports; 11,247 events were serious, and 15,204 events were non-serious. Of the 11,452 reports, 6026 (53%) were spontaneous and 5426 (47%) were noninterventional. The patient's age was provided in 8293 reports with a median age of 53 years and ranged from 1 day to 104 years.

Overall, the SOCs with the highest number of SAEs reported were: General disorders and administration site conditions, Infections and infestations, and Blood and lymphatic system disorders.

- The General disorders and administration site conditions SOC contained 2385 SAEs. The 3 most common PTs in this SOC were: death (n=804), adverse event (n=509), and pyrexia (n=212).
- The Infections and infestations SOC contained 1901 SAEs. The 3 most common PTs in this SOC were: pneumonia (n=279), sepsis (n=129), and septic shock (n=100).

- The Blood and lymphatic systems disorders SOC contained 763 SAEs. The 3 most common PTs in this SOC were: febrile neutropenia (n=235), neutropenia (n=150), and thrombocytopenia (n=100).

An analysis of the overall post-marketing data did not identify new safety concerns. The SAEs were generally consistent with manifestations or complications of the patient's underlying disease, reflected the critically ill nature of the patients who receive POS, were consistent with the known safety profile of the drug, had limited information, or contained information that confounded the assessment. Additionally, all reports of AEs, including the SAEs, are assessed on a continuing basis, as part of routine pharmacovigilance.

The MAH's global safety database was further queried for valid, spontaneous, and non-interventional study reports from market introduction for each formulation through 25-OCT-2024 for AEs reported in patients <18 years of age. A total of 1004 reports containing 2334 events were identified. Of these, 658 events were considered serious and 1676 were non serious. The median age was 9 years (range: 1 day to 17 years).

For patients <18 years of age, the SOCs with the highest number of SAEs reported were: Infections and infestations, General disorders and administration site conditions, and Nervous system disorders.

- The Infections and infestations SOC contained 105 SAEs. The 3 most common PTs in this SOC were: pneumonia (n=13), cytomegalovirus viraemia (n=9), and sepsis (n=9).
- The General disorders and administration site conditions SOC contained 86 SAEs. The 3 most common PTs in this SOC were: drug ineffective (n=14), drug interaction (n=14), and death (n=10).
- The Nervous system disorders SOC contained 66 SAEs. The 3 most common PTs in this SOC were: neurotoxicity (n=10), posterior reversible encephalopathy syndrome (n=9), and seizure (n=7).

An analysis of the post-marketing data available for patients <18 years of age did not identify any new safety concerns. The SAEs were generally consistent with manifestations or complications of the patient's underlying disease, reflect the critically ill nature of the patients who receive POS, were consistent with the known safety profile of the drug, had limited information, or contained information that confounded the assessment.

Distribution of SAEs Reported by SOC in Patients Less Than 18 Years of Age

SOC	**# Serious Events**	**% Serious Events**
Infections and infestations	105	15.96
General disorders and administration site conditions	86	13.07
Nervous system disorders	66	10.03
Gastrointestinal disorders	62	9.42
Respiratory, thoracic and mediastinal disorders	35	5.32
Hepatobiliary disorders	33	5.02
Metabolism and nutrition disorders	33	5.02

Blood and lymphatic system disorders	32	4.86
Investigations	29	4.41
Renal and urinary disorders	28	4.26
Skin and subcutaneous tissue disorders	25	3.80
Vascular disorders	19	2.89
Injury, poisoning and procedural complications	17	2.58
Cardiac disorders	16	2.43
Immune system disorders	16	2.43
Musculoskeletal and connective tissue disorders	12	1.82
Psychiatric disorders	12	1.82
Endocrine disorders	11	1.67
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9	1.37
Eye disorders	4	0.61
Surgical and medical procedures	3	0.46
Pregnancy, puerperium and perinatal conditions	2	0.30
Congenital, familial and genetic disorders	1	0.15
Ear and labyrinth disorders	1	0.15
Product issues	1	0.15
Total	658	100.00

The cumulative analysis of post-marketing AEs (including SAEs), as of 25-OCT-2024, did not identify any new safety concerns for POS overall and in paediatric patients. Based on this analysis, the safety profile in paediatric patients is consistent with the overall safety profiles. The MAH will continue to monitor the safety of POS through established routine pharmacovigilance processes.

The Committee noted that a cumulative analysis of post-marketing AEs, as of 25-OCT-2024, did not identify any new safety concerns for POS overall and in paediatric patients. Based on this analysis, the safety profile in paediatric patients is consistent with the overall known safety profile.

2.5.1. Discussion on clinical safety

POS was generally well tolerated in paediatric participants aged 2 to <18 years with IA as both IV and oral (PFS or tablet) formulations. No new safety signals were identified during study P104. In the study, POS was shown to be well tolerated and associated with high clinical response rates in paediatric participants aged 2 to <18 years with IA.

The safety profile of POS in this study was consistent with the participants' underlying disease and treatment, and the known safety profile of the drug. The AE rates reported in study P104

compared favourably with POS and VOR in the adult pivotal Phase 3 study MK-5592- 069, which showed the non-inferiority of POS to VOR in adult participants with IA. Rates of SAEs, AEs leading to death, and AEs leading to discontinuation of study intervention in this study were comparable with MK-5592-069.

2.5.2. Conclusions on clinical safety

Based on the data provided by the MAH corresponding to the final results of P104-MK5592 study, no new safety concerns have been identified as compared to previous studies and clinical experiences gained in adults and children from 2 years of age treated with POS.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version 18.1 (data lock point 25 October 2024, dated 19 February 2025) with this application to support the extension of the indication for treatment of invasive aspergillosis for Noxafil IV, tablet, and PFS formulations to include paediatric patients 2 years of age and older. The proposed RMP main changes were the following:

RMP Section	Changes
PART I: Product(s) Overview	Updated to extend the indication for Noxafil (IV, Tablet and PFS formulations) for treatment of invasive aspergillosis in paediatric patients from 2 to < 18 years of age
PART II: MODULE SIII - Clinical trial exposure	Updated overall exposure and demographic information
PART II: MODULE SV – Post-Authorization Experience	Updated patient exposure data

Safety concerns

Module SVIII Summary of the Safety Concerns

Table SVIII.1 Summary of the Safety Concerns

Summary of Safety Concerns	
Important identified risks	None*
Important potential risks	Injury, Poisoning, and Procedural Complications - Medication error related to substitution between different formulations (oral suspension and PFS)*
Missing information	Safety in children below 2 years of age

* The important identified or potential risks included in prior versions of the RMP have been removed based the review of accumulating clinical data and the guidance in GVP module 5 (Rev 2), as per routine updates of the RMP during the life cycle of the product.

The safety concerns remain unchanged. This was acceptable to the Committee.

Version 19 of the RMP is approved with this variation.

Pharmacovigilance plan

PART III PHARMACOVIGILANCE PLAN

There are no ongoing and planned category 1-2 and 3 studies for Noxafil. As part of the routine pharmacovigilance activities, the Company uses event-specific questionnaires to obtain structured information about the following events: hepatic disease, cardiac arrhythmia, QT prolongation, adrenal insufficiency, seizure/convulsion, venous thromboembolism, myocardial infarction, neutropenia/agranulocytosis, cerebrovascular accident, and drug adverse experience.

The MAH has been removed the PN104 study from the Additional Pharmacovigilance Activities. This is endorsed.

The Committee considered that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for posaconazole. The was accepted by the Committee.

Risk minimisation measures

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

A one-time DHPC regarding the potential risk of Medication error related to substitution between different formulations (oral suspension and Gastro-Resistant Powder and Solvent for Oral Suspension) will be disseminated to the EEA countries that market both the oral suspension and PFS at the time of launch of the new PFS formulation. The DHPC will inform healthcare professionals about the new PFS formulation and the potential risk of medication errors as a result of prescriber confusion between the formulations.

The proposed routine risk minimisation measures and additional risk minimization measures are sufficient to minimise the risks of the product in the proposed indication(s).

During this procedure, an updated version of the RMP (version 19) in support the extension of the indication for treatment of invasive aspergillosis for Noxafil IV, tablet, and PFS formulations to include pediatric patients 2 years of age and older was provided, in which the targeted questionnaires associated to the safety concerns that were removed from the RMP (to align with GVP module V Revision 2), as previously agreed by the PRAC.

2.7. Update of the Product information

With this variation, SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the IV, gastro-resistant tablet and powder for suspension (PFS) formulations were proposed to be updated. The Package Leaflet and Labelling were proposed to be updated in accordance.

In section 4.1 of the gastro-resistant tablet SmPC, the indication for IA in adults was extended to children from 2 years of age and weighing 40 kg, which is acceptable.

In section 4.1 of the IV formulation SmPC, the indication for IA in adults was extended to children from 2 years of age, with IV dosing recommendation in section 4.2, following the body-weight dosing of 6 mg/kg BID the first day followed by 6 mg/kg thereafter, which is acceptable.

In section 4.1 of the powder for suspension (PFS) SmPC, the indication for IA in adults was extended to children from 2 years of age, which is acceptable.

Given this procedure's context is paediatric use, when assessing the proposed PI amendments, the CHMP also agreed that carrying out a thorough review of the paediatric information throughout all existing formulations and corresponding SmPCs was necessary to enhance the overall PI readability. The CHMP considered that optimizing the PI was crucial, mainly because this extension of indication does not apply to the Noxafil oral suspension (an otherwise suitable paediatric formulation), which cannot be recommended in children.

As a consequence of the assessment, the Product Information resulted also in changes to sections 4.4 and 4.5.

For section 5.2, regardless of the formulation, results from the study were included in addition to the results from the PPK analysis (no effect of age, sex, renal impairment, ethnicity, and disease status) this is acceptable.

The Marketing authorisation holder (MAH) also took the opportunity to implement editorial changes to the PI. In addition, the list of local representatives in the PL has been revised to amend contact details for a number of representatives.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

In this submission, the changes to the package leaflet for Noxafil are limited. The only changes in the patient leaflet text are revisions of the paragraphs concerning the paediatric indication, i.e. section "1. What Noxafil is and what it is used for" and few minor editorial and administrative changes. There are no other proposed changes to the content of the package leaflet; in particular, the key messages for the safe use of the medicinal product are not impacted. Furthermore, the design, layout and format of the package leaflet will not be affected by the proposed revisions. Therefore, the MAH considers that these proposed revisions do not constitute significant changes that would require the need to conduct a new user consultation.

2.7.2. Additional monitoring

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Invasive aspergillosis (IA)

Aspergillus species are filamentous fungi, commonly found in the environment, that can cause a wide spectrum of infections in humans; these infections can be acute and life-threatening, primarily in immunocompromised individuals.

IA infections occur in paediatric (and adult) populations that are immunocompromised due to various factors (e.g., malignancy, solid organ transplant or hematopoietic stem cell transplant, and primary immunodeficiency) and play a significant role in the morbidity and mortality observed in these populations. A retrospective cohort study reported that the incidence of IA among hospitalized immuno-compromised children <18 years of age in the US was between 0.1% and 30%. A 2021 study in the EU estimated the prevalence of IA among immunocompromised children to be 2.2%. Following an initial diagnosis of IA, immunocompromised children in the US had a 12-week and 1-year all-cause mortality rate of 25.4% and 40.7%, respectively, in 2019.

3.1.2. Available therapies and unmet medical need

Current guidelines for the management and treatment of IA in adult patients recommend Voriconazole as the primary treatment of IA, with POS, isavuconazole, liposomal AMB, and echinocandins as alternative or second line therapies.

Despite the availability of some antifungals for the treatment of IA in paediatric patients, these therapeutic options are associated with toxicities and drug-drug interactions. Therefore, there is an unmet medical need for additional safe and effective alternative therapies for the management of this potentially life-threatening infection. While Posaconazole belongs to an existing pharmacological class, the availability of IV and oral formulations together with some potential differential level of activity as compared to other azoles is of value for the therapeutic management of children.

3.1.3. Main clinical studies

Given the similarity of the disease, the principle of PK extrapolation with similar exposure as in adults to predict efficacy and safety is acknowledged for establishing dosing in paediatric patients for antifungal treatment. PK and safety data, together with some descriptive efficacy data have been derived from the submitted final study report for Study P104-MK5592**.**

- P104MK5592: A Phase 2, Open-Label, Non-Comparative Clinical Trial to Study the Safety and Efficacy of Posaconazole (POS, MK-5592) in Paediatric Participants Aged 2 to Less Than 18 Years With Invasive Aspergillosis (IA).

3.2. Favourable effects

As regards the PK data (pivotal) to support extrapolation from adults' efficacy and safety to paediatric population:

The PPK model used in support of this extension of indication shared the same structure as previously described for study P097 and consisted of a compartmental (cpt) model parameterized in terms of CL, Vc, ka and F (bioavailability, logit function).

The PK data of study P104, supports the use of POS IV, PFS and tablet in paediatric patients aged 2-<18 years for the treatment of IA.

As regards the clinical data:

Results derived from the study P104MK5592, 31 patients were included. The median age for Age Cohort 1 was 8.0 years old (2 to 11 years) and for Age Cohort 2 was 14.0 years old (12 to 17 years). Chronic (≥30 days' duration) IA, relapsed/recurrent IA, or refractory IA that had not responded to prior antifungal treatment were excluded of the study.

The majority (67.7%, 95% CI: 48.6, 83.3) of participants in the FAS population achieved a favourable global clinical response (success) through Week 6. A greater percentage of participants achieved a favourable global clinical response through Week 12 (77.4%, 95% CI: 58.9, 90.4) compared with Week 6. The percentage of participants who achieved complete response increased from 29.0% through Week 6 to 48.4% through Week 12.

No participant in the 25 responder patients had a relapse of IA through 28 days post-treatment.

Most participants (90%) reported PFS as tasting "very good," "good," or "neither good nor bad" on the first and last days of PFS. None of the participants reported any problems taking the PFS dose.

3.3. Uncertainties and limitations about favourable effects

Efficacy data can only be considered supportive of the PK data that allowed extrapolation of the clinical data available in adults with IA to the paediatric population, considering methodological limitations (i.e. open-label, non-comparative study with safety as primary endpoint and a limited sample size) and the fact that no microbiological confirmation of IA was implemented.

3.4. Unfavourable effects

The most frequently reported drug-related AEs (6.5%) were ALT and AST increased, both reported for 2 participants in Age Cohort 2. A drug-related AE meeting the criteria for an ECI (liver function test increased) was reported for 1 participant in Age Cohort 2 (for a potential DILI event).

Deaths due to AEs were reported for 4 (12.9%) participants during the study. There was one death in Age Cohort 1 due to leukemic infiltration extramedullary and three deaths in Age Cohort 2 due to pulmonary haemorrhage, hematemesis, and thrombocytopenia. None of the deaths were considered drug-related by the investigator.

SAEs were reported for 12 (38.7%) participants. The 2 most frequently reported SAEs (6.5%) were febrile neutropenia and sepsis. No SAEs were considered drug-related by the investigator.

Overall, two participants (1 in each age cohort) had a QTc value ≥500 msec during the treatment phase. The prolonged QTc values in both participants resolved. Both participants remained on study intervention without interruption and completed the study. One participant did not have this event reported as an AE, and the other participant had "electrocardiogram QT prolonged" reported twice as an AE that was not considered drug related by the investigator. Given that posaconazole is known as being associated with QT prolongation, the MAH provided extra relevant data for these two non-serious AEs of "electrocardiogram QT prolonged." Both AEs were considered not related, and the outcome was "recovered".

3.5. Uncertainties and limitations about unfavourable effects

Safety data from P104 demonstrate that POS is generally well tolerated in paediatric participants aged 2 to <18 years with IA. However, a drug-related AE meeting the criteria for an ECI (liver function test increased) was reported for 1 participant in Age Cohort 2 (for a potential DILI event) which was resolved.

3.6. Effects Table

Table 30: Effects Table for Noxafil in the treatment of IA in paediatric patients aged 2 to < 18 years.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Global clinical response at 6 weeks and 12 weeks	EORTC definition	% %	67.7 77.4	NA	[48.6, 83.3] [58.9, 90.4]	P104
Number of Relapse at 28 days post-treatment		%	0/25	NA		P104
Palatability		%	90	NA		P104
Unfavourable Effects						
Hepatic Safety events	ASAT increased ALAT increased Liver function test increased	%	POS IV or PFS or tablet	No control	6.5% 6.5% 3.2%	P104
Cardiac events	QTc value ≥500 msec	%	POS IV or PFS or tablet	No control	6.5%	P104
Other events	Gastrointestinal disorders Feeling hot Infusion site reaction	%	POS IV or PFS or tablet	No control	6.5% 3.2% 3.2%	P104

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Given the similarity of the disease, the principle of PK extrapolation with similar exposure as in adults to predict efficacy and safety is acknowledged for establishing dosing in paediatric patients for antifungal treatment. PK and safety data, together with some descriptive efficacy data have been derived from study P104-MK5592.

In terms of PK, the PPK model is based on a large cohort of paediatric subjects across three studies with age ranging from 8 months to 17 years, BW from 5.5 to 102 kg (for P104, BW: 12-65 kg).

The PPK model shared the same structure as previously described for study P097 and consisted of a 1 cpt model parameterized in terms of CL, Vc, ka and F (bioavailability, logit function).

Overall, PK parameters were estimated with good precision, GOF does not show a particular bias and pcVPC shows reasonably adequate predictive performance. Comparisons between the predicted Cmax and Cmin by the PPK model with the observed Cmax and Ctrough for the IV and oral formulations, indicate similar results, confirming the adequacy of the developed PPK model.

As regards the clinical data derived from the study P104-MK5592:

Among the 31 included 2 to 18 aged patients, the majority (67.7%, 95% CI: 48.6, 83.3) of participants in the FAS population achieved a favourable global clinical response (success) through Week 6. A greater percentage of participants achieved a favourable global clinical response through Week 12 (77.4%, 95% CI: 58.9, 90.4) compared with Week 6. The percentage of participants who achieved complete response increased from 29.0% through Week 6 to 48.4% through Week 12. Albeit descriptive data, those results well compare favourably to the efficacy data derived from the well-designed pivotal study in adults in the same indication.

No participant in the 25 responder patients had a relapse of IA through 28 days post-treatment.

Most participants (90%) reported PFS as tasting "very good," "good," or "neither good nor bad" on the first and last days of PFS. None of the participants reported any problems taking the PFS dose.

Safety data from P104 demonstrate that POS is generally well tolerated in paediatric participants aged 2 to <18 years with IA. No new safety concerns have been identified as compared to previous studies and clinical experiences gained in adults and children from 2 years of age treated with POS.

3.7.2. Balance of benefits and risks

The balance of benefits and risk for the extension of indication of treatment of IA as first-line therapy to include patients aged 2 years and older is considered positive as satisfactory clarifications were provided on PK and safety parts of the dossier.

3.8. Conclusions

The overall B/R of NOXAFIL as first-line therapy treatment of IA in paediatric subjects from 2 to 18 years old is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	II	I and IIIB

Extension of indication for NOXAFIL to include treatment of patients two years of age and older for invasive aspergillosis (IA) based on final results from study MK-5592-104 (P104); this is a Phase 2, open-label, noncomparative clinical study that evaluated the safety, efficacy, and PK of POS in paediatric participants aged 2 to <18 years with IA. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet was updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the PI and to revise the list of local representatives in the PL to amend contact details for a number of representatives. Version 19 of the RMP is approved with this variation.

The variation leads to amendments to the annexes I, IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, IIIB and to the Risk Management Plan are recommended.

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

- **Risk management plan (RMP)**

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

In addition, 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 P/0376/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP, by consensus, is of the opinion that Noxafil is not similar to Cresemba within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Noxafil EMEA-H-000610-VR/0000263360'