22 August 2024
EMA/420915/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Noxafil

Posaconazole

Procedure no: EMEA/H/C/000610/P46/031

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of procedure	24 Jun 2024	24 Jun 2024
☐	CHMP Rapporteur Assessment Report	29 Jul 2024	31 Jul 2024
☐	CHMP members comments	12 Aug 2024	12 Aug 2024
☐	Updated CHMP Rapporteur Assessment Report	16 Aug 2024	16 Aug 2024
☒	CHMP adoption of conclusions:	22 Aug 2024	22 Aug 2024

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1. Introduction

On 07-jun-2024, the MAH submitted a completed paediatric study for NOXAFIL, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure-P46/031

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

NOXAFIL posaconazole is approved for prophylaxis and salvage treatment of invasive fungal infection in adult and paediatric patients 2 to <18 years of age. It is also approved for the primary treatment of IA but only in adults. Currently approved NOXAFIL (POS) formulations include an IV solution and 3 oral formulations (an oral suspension, a gastro-resistant Powder For Oral Suspension [PFS], and a tablet).

The MAH stated that the paediatric clinical development program, including the present study P104 is described in the PIP (PIP000468-PIP02-12-M08). The P104 study was conducted to evaluate the safety, efficacy, and PK of NOXAFIL IV and oral formulations in paediatric participants 2 to <18 years of age with IA, as defined by EORTC/MSG consensus disease definitions.

The MAH is reviewing the results and intends to submit a type II variation in Q1 2025, consisting of the full relevant data package with amendments, to extend the indication to paediatric patients 2 years and older for the treatment of invasive aspergillosis.

2.2. Information on the pharmaceutical formulation used in the study

The following study medications will be used in the trial:

- Posaconazole solution for infusion (IV)
- Posaconazole powder for oral suspension (PFS)
- Posaconazole tablets

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

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

2.3.2. Clinical study

P104MK5592

Description

This is a Phase 2, Open-Label, Non-Comparative Clinical Trial to Study the Safety and Efficacy of Posaconazole (POS, MK-5592) in Pediatric 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 (eg, 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:

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.

Objective(s) and Outcomes/endpoints

The objectives and endpoints are presented in the table below:

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

Sample size

The planned enrollment 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)

Open-label, non-comparative study.

Statistical Methods

Key elements of the statistical analysis plan are summarized below

Study Design Overview	A Phase 2, Open-Label, Non-Comparative Clinical Trial to Study the Safety and Efficacy of Posaconazole (POS, MK-5592) in Pediatric Participants Aged 2 to <18 Years With Invasive Aspergillosis
Treatment Assignment	Pediatric participants aged 2 to <18 years with IA will be allocated to receive POS (Day 1-7 IV formulation, Day 8-84 either IV, PFS or oral formulation). Participants will be enrolled into two age cohorts: Age Cohort 1 (2 to <12 years) or Age Cohort 2 (12 to <18 years).
Analysis Populations	**Safety**: All Participants as Treated (APaT). **Efficacy**: • Full Analysis Set (FAS) and • Responder Population. **Pharmacokinetics**: All treated participants who receive at least 7 days of POS IV solution and complete PK sampling through Day 7 (Primary PK Population). Analysis populations are defined in Section 9.5.
Primary Endpoint(s)	The primary safety endpoint is the proportion of participants in the APaT population who experience 1 or more treatment-related AEs during POS study treatment (IV or oral) plus 14 days of follow-up. There are no primary efficacy or pharmacokinetic endpoints.
Key Secondary Endpoints	• Proportion of participants in the FAS population with a favorable global clinical response (partial or complete response) at the Week 6 (Day 42) Visit, at the Week 12 (Day 84) Visit, and at the EOT Visit (if different). • Proportion of participants in the Responder Population who have a relapse of IA at any point after achieving favorable global clinical response through 28 days post-treatment. • C_{avg}, C_{min}, C_{max}, AUC, and T_{max}, estimated by population PK analysis. • Analysis of exposure-response (efficacy and safety) relationships. • Participants' categorical perception of palatability and acceptability of the PFS formulation.

There are no hypotheses in this study.

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.

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 decision. About half the participants (47.1%) in Age Cohort 2 discontinued study intervention prior to Week 12; the most common reasons were physician 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 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.

	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)

Recruitment

First Participant enrolled: 02-JUL-2020

Last participant last visit: 18-DEC-2023

Baseline data

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 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.

Number 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.

Efficacy results

- **Global Clinical Response Through Week 6 and Week 12** (Full Analysis Set Population) is presented in the table below

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.

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)

- **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 leukemic infiltration extramedullary so relapse of IA through 28 days post-treatment was not assessed.

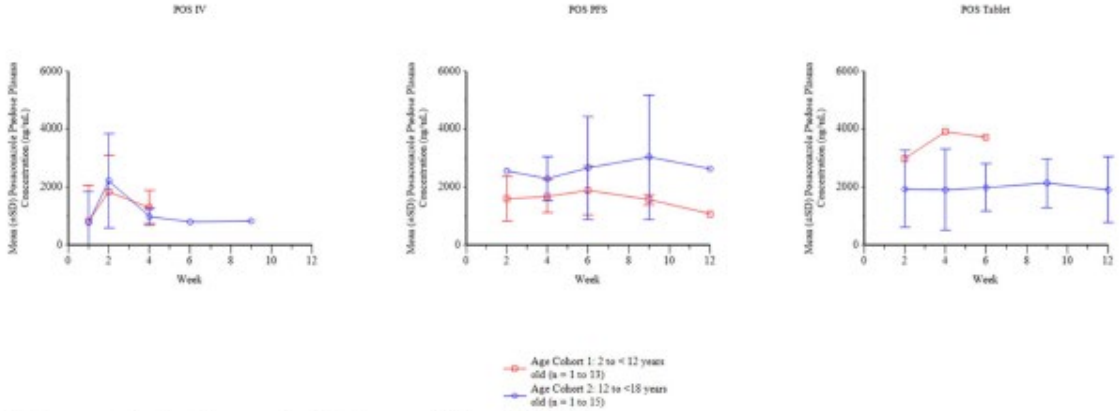
Pharmacokinetic Results:

The primary PK population included 28 (13 in Age Cohort 1 and 15 in Age Cohort 2) participants who had at least 1 postdose plasma concentration obtained after receiving at least 5 days of treatment with any POS formulation. In the provided report descriptive statistics were determined for POS plasma concentrations at each time point for all participants stratified by age cohort and POS formulation.

Mean POS predose (trough) plasma concentrations were generally similar with values of approximately 1000-2000 ng/mL across the 3 formulations (IV, PFS, tablet) and between the 2 age cohorts as illustrated below.

A population PK analysis will be conducted based on population PK models from prior paediatric PK data for each formulation. PK parameters for POS (Cmax, Cmin, Cavg, AUC, and Tmax) derived from the population PK analysis will be reported in a separate modelling and simulation report. An analysis of exposure-response (efficacy and safety) relationship, as available data allow, will be conducted as part of the population PK analysis, and will also be reported separately.

Figure 14.2-1
Arithmetic Mean (±SD) Predose (Trough) Plasma Concentration vs Time Profiles of Posaconazole When Administered in Pediatric Participants Aged 2 to Less Than 18 Years With Invasive Aspergillosis by Age Cohort and Formulation (Linear Scale)



IV = Intravenous; PFS = Powder for suspension; POS = Posaconazole; SD = standard deviation.

Assessor's Comments:

Only sparse sampling was planned for the PK investigation. Therefore, the descriptive statistics derived from it could only sought as indicative and no reliable conclusions could be drawn from it. The applicant is planning an integrative analysis of the available data through the development of a population-PK model. The aim is to allow elucidation of PKs of Posaconazole in paediatric patients and identify the covariates influencing it. This model, if developed successfully, will allow prediction of systemic exposure in paediatric patients. Based on these predictions, the Exposure-Response relationship will be also explored in order support the dosing scheme in infants.

The planned analysis is agreed. It is expected that those data will be submitted in support of the forthcoming type II variation to extend the indication in children from 2 years of age.

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.

All-cause Mortality

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.

Assessor comments

In P104, 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≥1 postallocation observation for the analysis endpoint after ≥1 dose of study intervention, and had baseline data for those analyses that require baseline data.

The majority (67.7%, 95% CI: 48.6, 83.3) of participants in the FAS population achieved a favorable global clinical response (success) through Week 6. A greater percentage of participants achieved a favorable 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.

Among participants with possible IA (n=22):

- The percentage of participants with a favorable global clinical response through both time periods (Week 6 and Week 12) was 68.2% (n=15),
- The percentage of participants with an unfavorable global clinical response through both time periods was 22.7% (n=5),
- The percentage of participants with an unfavorable global clinical response through Week 6 but a favorable 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 favorable global clinical response through both time periods was 71.4% (n=5), and
- The percentage of participants with an unfavorable global clinical response through both time periods was 28.6% (n=2).

Among participants with proven IA (n=2):

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

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

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.

Overall, these results are consistent with the efficacy results observed in the previous studies performed. However, no formal conclusion on efficacy in this population can be made since the study was not designed for that (open-label, non-comparative study with safety as primary endpoint and a

limited sample size). In any case it is acknowledged that the efficacy/safety in children is to be predicted based on similar PK exposure in adults.

Safety results

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, regardless of their IA classification. All AEs were reported from the time of intervention allocation through 14 days following cessation of treatment. Survival assessment was reported through Day 114.

Brief Summary of AEs

As anticipated for this severely ill population with IA, AEs were reported for most of the participants (87.1%) in the APaT population. Overall, 22.6% of participants had AEs that were considered drug-related by the investigator.

SAEs were reported for 38.7% of participants; none of the SAEs were considered drug-related by the investigator. Four participants (12.9%) had AEs resulting in death during the study; none of the deaths were considered drug-related by the investigator.

Two (6.5%) participants discontinued study intervention due to an AE: 1 in Age Cohort 1 with a fatal outcome (leukemic infiltration extramedullary) and 1 in Age Cohort 2, which was an ECI and resolved (liver function test increased).

Most Frequently Reported AEs

The 4 most frequently reported AEs were vomiting (32.3%), pyrexia (29.0%), hypertension (25.8%), and abdominal pain (19.4%).

Among 8 (25.8%) participants with an AE of hypertension, none were considered drug related by the investigator, study intervention was continued without interruption, and all events resolved. Three of the 8 participants also had AEs of hypokalemia co-reported with hypertension during the treatment period. Hypokalemia was reported after hypertension for 1 participant (5 days later), and before hypertension for 2 participants (4 days prior and 12 days prior, respectively). No cases of hypokalemia were considered drug-related by the investigator, and study intervention was continued without interruption during these events. All events were considered non-serious; hypokalemia was resolved for 2 of the 3 participants while still on study intervention, but not resolved for 1 participant.

The most frequently reported drug-related AEs (6.5%) were ALT increased and AST increased, both in 2 participants in Age Cohort 2. All drug-related AEs were Grades 1 or 2 in severity and resolved.

The 2 most frequently reported SAEs (6.5%) were febrile neutropenia and sepsis.

Confounding factors were noted among all 3 participants, all of whom were hospitalized with complicated oncologic histories.

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[a] 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)

[a] 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.

Source: [P104MK5592: adam-adsl; adae]

Classification of Adverse Events

Related to Study Intervention

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.

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

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.

Toxicity Grade of Adverse Events

Overall, approximately one-third of participants had AEs with maximum Grades 1 or 2 severity.

Approximately one-third of participants had maximum Grade 3 AEs. The most frequently reported (>2 participants in both age cohorts combined) Grade 3 AEs was febrile neutropenia.

Two (6.5%) participants had maximum Grade 4 AEs. One participant in Age Cohort 1 had gastroenteritis clostridial that was not considered drug-related by the investigator and resolved; another participant in Age Cohort 2 had pneumonia, adenovirus infection, and viral sepsis that were not considered drug-related by the investigator and resolved.

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

Serious Adverse Events

Deaths Due to Adverse Events

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 hemorrhage, hematemesis, and thrombocytopenia. None of the deaths were considered drug-related by the investigator.

Other Serious Adverse Events

Overall, 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. One participant in Age Cohort 1 discontinued study intervention due to an SAE (leukemic infiltration extramedullary) with a fatal outcome.

Discontinuation Due to Adverse Events

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

AEs of Special Interest

A drug-related AE meeting the criteria for an ECI (liver function test increased) was reported for 1 participant in Age Cohort 2. This participant discontinued study intervention due to the event. The event was considered drug-related by the investigator and resolved; the participant completed the study.

Clinical Laboratory Evaluation

No clinically meaningful changes were observed in any laboratory parameters from baseline over time for both age cohorts. For the majority of participants, there were no clinically meaningful findings in laboratory values (hematology and chemistry) that met predefined limits of change criteria based on Common Terminology Criteria for Adverse Events version 5.0. Hepatic laboratory findings that met predetermined criteria showed that the majority of participants in both age cohorts combined had elevations in ALT or AST (67.8%), while a smaller percentage of participants had elevations in bilirubin (16.1%) and alkaline phosphatase (12.9%).

Vital Signs and Other Observations Related to Safety

No clinically meaningful changes were observed in mean changes in vital sign measurements (ie, 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 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. Confounding factors were noted among both participants.

Safety Results Summary

In pediatric participants aged 2 to <18 years with IA who received POS:

Overall AEs

- AEs were reported for most of the participants in the APaT population (85.7% in Age Cohort 1 and 88.2% in Age Cohort 2).
- 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). All drug-related AEs were Grades 1 or 2 in severity and resolved.

SAEs and Other Clinically Meaningful AEs

- Deaths due to AEs were reported for 4 (12.9%) participants during the study. 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.
- Two participants discontinued study intervention due to an AE.
    - One participant in Age Cohort 1 due to an SAE (leukemic infiltration extramedullary) with a fatal outcome.
    - One participant in Age Cohort 2 due to an AE (liver function test increased), which was considered drug-related by the investigator and met criteria for an ECI. The event resolved and the participant completed the study.
- 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.

Safety data from P104 demonstrate that POS is generally well tolerated in pediatric participants aged 2 to <18 years with IA. No new safety concerns were identified in pediatric participants from P104.

Assessor comments

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.

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 hemorrhage, 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. Safety data from P104 demonstrate that POS is generally well tolerated in pediatric participants aged 2 to <18 years with IA. No new safety concerns were identified in pediatric participants from P104.

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.

2.3.3. Discussion on clinical aspects

Overall, the clinical response rates results are consistent with those observed in the previous studies performed. However, based on this study results alone, no formal conclusion on efficacy in this paediatric population can be made since the study was not designed for this (open-label and non-comparative study with safety as primary endpoint and a limited number of subjects enrolled). In any case it is acknowledged that the efficacy/safety in children is to be predicted based on similar PK exposure in adults.

POS was generally well tolerated in pediatric participants aged 2 to <18 years with IA as both IV and oral (PFS or tablet) formulations. No new safety signals were identified during the study.

In this study, POS was shown to be well tolerated and associated with high clinical response rates in pediatric 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 this study compared favorably 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.

3. Rapporteur's overall conclusion and recommendation

Based on the data provided by the MAH regarding the final results of P104MK5592 study, no new safety or efficacy concerns have been identified as compared to previous studies and experiences in adults and children from 2 years of age treated with POS.

No change to the Product Information (PI) for Noxafil based on this paediatric study is claimed by the MAH however the MAH is reviewing the results and intends to submit a type II variation in Q1 2025, consisting of the full relevant data package with amendments, to extend the indication to paediatric patients 2 years and older for the treatment of invasive aspergillosis.

☒ Fulfilled:

No regulatory action required.